



10/049266  
JC07 Rec'd PCT/PTO 11 FEB 2002

TRANSMITTAL LETTER TO THE UNITED STATES ATTORNEY'S DOCKET NUMBER 50559

DESIGNATED/ELECTED OFFICE (DO/EO/US)  
CONCERNING A FILING UNDER 35 U.S.C. 371

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/07440	1 August 2000	9 August 1999

TITLE OF INVENTION: NOVEL ANTAGONISTS OF INTEGRIN RECEPTORS

APPLICANT(S) FOR DO/EO/US Andreas KLING, Herve GENESTE, Udo LANGE, Arnulf LAUTERBACH, Claudia Isabella GRAEF, Thomas SUBKOWSKI, Uta HOLZENKAMP, Helmut MACK, Jens SADOWSKI, Wilfried HORNBERGER, Volker LAUX

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. /X/ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
  2. / / This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
  3. /X/ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
  4. /X/ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
  5. /X/ A copy of the International Application as filed (35 U.S.C. 371(c)(2)).
    - a./X/ is transmitted herewith (required only if not transmitted by the International Bureau).
    - b./ / has been transmitted by the International Bureau.
    - c./ / is not required, as the application was filed in the United States Receiving Office (RO/USO).
  6. /X/ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
  7. / / Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
    - a./ / are transmitted herewith (required only if not transmitted by the International Bureau).
    - b./ / have been transmitted by the International Bureau.
    - c./ / have not been made; however, the time limit for making such amendments has NOT expired.
    - d./ / have not been made and will not be made.
  8. / / A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
  9. / / An oath or declaration of the inventor(s) (35 U.S.C. 171(c)(4)).
  10. / / A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).
- Items 11. to 16. below concern other document(s) or information included:
11. / / An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
  12. / / An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
  13. /X / A FIRST preliminary amendment.  
/ / A SECOND or SUBSEQUENT preliminary amendment.
  14. / / A substitute specification.
  15. / / A change of power of attorney and/or address letter.
  16. /X / Other items or information.  
International Search Report  
International Preliminary Examination Report

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U.S. Appl. No. (If Known) INTERNATIONAL APPLN. NO.  
PCT/EP00/07440ATTORNEY'S DOCKET NO.  
50559

17. /X/ The following fees are submitted  
 BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)):  
 Search Report has been prepared by the  
 EPO or JPO.....\$890.00

**CALCULATIONS****PTO USE ONLY**

International preliminary examination fee paid to USPTO  
 (37 CFR 1.482).....\$710.00

No international preliminary examination fee paid to  
 USPTO (37 CFR 1.482) but international search fee paid  
 to USPTO (37 CFR 1.445(a)(2)).....\$740.00

Neither international preliminary examination fee  
 (37 CFR 1.482) nor international search fee  
 (37 CFR 1.445(a)(2)) paid to USPTO .....\$1,040.00

International preliminary examination fee paid to  
 USPTO (37 CFR 1.482) and all claims satisfied pro  
 -visions of PCT Article 33(2)-(4).....\$100.00

**ENTER APPROPRIATE BASIC FEE AMOUNT = \$ 890.00**

Surcharge of \$130.00 for furnishing the oath or declaration  
 later than // 20 // 30 months from the earliest  
 claimed priority date (37 CFR 1.492(e)).

Claims	Number Filed	Number Extra	Rate
Total Claims	11	-20	X\$18.
Indep. Claims	1	-3	X\$84.
Multiple dependent claim(s)(if applicable)			+280.
<b>TOTAL OF ABOVE CALCULATION</b>			<b>= 890.</b>

Reduction of 1/2 for filing by small entity, if applicable.  
 Verified Small Entity statement must also be filed  
 (Note 37 CFR 1.9, 1.27, 1.28).

**SUBTOTAL = 890.**

Processing fee of \$130. for furnishing the English  
 translation later than // 20 // 30 months from the  
 earliest claimed priority date (37 CFR 1.492(f)). +

**TOTAL NATIONAL FEE = 890.**

Fee for recording the enclosed assignment (37 CFR 1.21(h)).  
 The assignment must be accompanied by an appropriate cover  
 sheet (37 CFR 3.28, 3.31) \$40.00 per property =

**TOTAL FEES ENCLOSED = \$ 890.00**

Amount to be  
 refunded: \$  
 Charged \$

a./X/ A check in the amount of \$ 890.00 to cover the above fees is enclosed.

b./ / Please charge my Deposit Account No. \_\_\_\_\_ in the amount of \$ \_\_\_\_\_ to cover the above fees. A duplicate copy of this sheet is enclosed.

c./X/ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 11-0345. A duplicate copy of this sheet is enclosed.

**NOTE:** Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b) must be filed and granted to restore the application to pending status.

**SEND ALL CORRESPONDENCE TO:**  
 KEIL & WEINKAUF  
 1101 Connecticut Ave., N.W.  
 Washington, D. C. 20036

*Herbert B. Keil*  
 SIGNATURE

Herbert B. Keil

NAME

Registration No. 18,967

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of )  
KLING et al. ) BOX PCT  
)  
International Application )  
PCT/EP 00/07440 )  
)  
Filed: August 1, 2000 )  
)

For: NOVEL ANTAGONISTS OF INTEGRIN RECEPTORS

PRELIMINARY AMENDMENT

Honorable Commissioner of  
Patents and Trademarks  
Washington, D.C. 20231

Sir:

Prior to examination, kindly amend the above-identified application as follows:

IN THE CLAIMS

Cancel claims 9, 10 and 11.

Kindly amend the claims as shown on the attached sheets.

R E M A R K S

The claims have been amended to eliminate multiple dependency and to place them in better form for U.S. filing. No new matter is included.

Favorable action is solicited.

Respectfully submitted,

KEIL & WEINKAUF



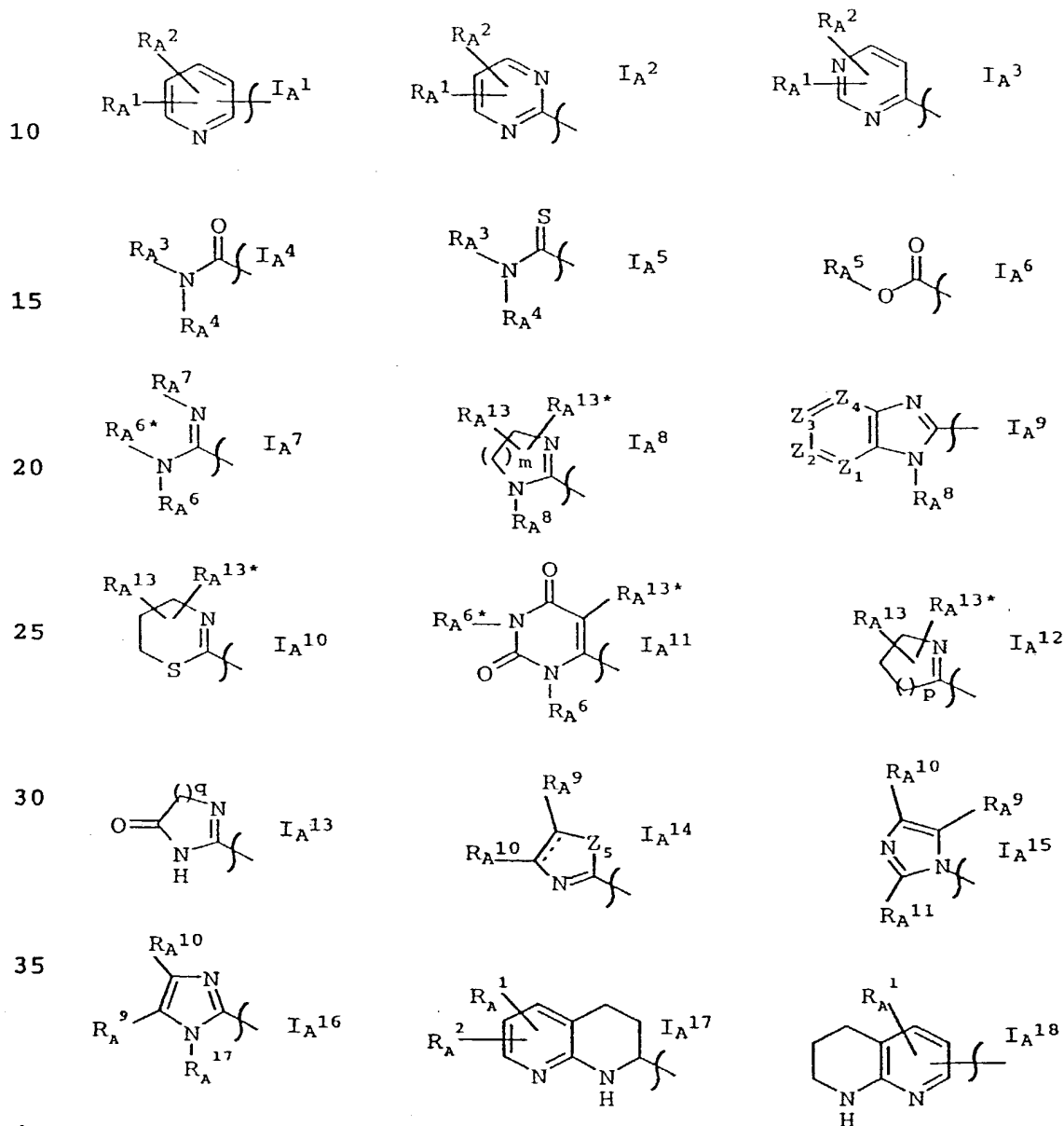
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(202)659-0100

3. A compound as claimed in claim 1, wherein the structural element used as structural element A is selected from the group of structural elements of the formulae I<sub>A</sub><sup>1</sup> to I<sub>A</sub><sup>18</sup>,

5



where

m, p, q

are, independently of one another, 1, 2 or 3,

45



$R_A^{11}$ ,  $R_A^{12}$

are, independently of one another, hydrogen, CN, halogen,  
a branched or unbranched, optionally substituted  
C<sub>1</sub>-C<sub>6</sub>-alkyl or CO-C<sub>1</sub>-C<sub>6</sub>-alkyl radical or an optionally  
substituted aryl, arylalkyl, hetaryl, hetarylalkyl or  
C<sub>3</sub>-C<sub>7</sub>-cycloalkyl radical or a radical CO-O- $R_A^{14}$ , O- $R_A^{14}$ ,  
S- $R_A^{14}$ ,  $NR_A^{15}R_A^{16}$ , CO- $NR_A^{15}R_A^{16}$  or SO<sub>2</sub> $NR_A^{15}R_A^{16}$  or the two  $R_A^{11}$   
and  $R_A^{12}$  radicals together are a fused-on, optionally  
substituted 5- or 6-membered, unsaturated or aromatic  
carbocyclic or heterocyclic system which may contain up  
to three heteroatoms selected from the group of O, N, or  
S,

$R_A^{13}$ ,  $R_A^{13*}$

are, independently of one another, hydrogen, CN, halogen,  
a branched or unbranched, optionally substituted  
C<sub>1</sub>-C<sub>6</sub>-alkyl radical or an optionally substituted aryl,  
arylalkyl, hetaryl, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl radical or a  
CO-O- $R_A^{14}$ , O- $R_A^{14}$ , S- $R_A^{14}$ ,  $NR_A^{15}R_A^{16}$  or CO- $NR_A^{15}R_A^{16}$  radical,

where

$R_A^{14}$  is hydrogen, a branched or unbranched, optionally  
substituted C<sub>1</sub>-C<sub>6</sub>-alkyl, alkylene-C<sub>1</sub>-C<sub>4</sub>-alkoxy,  
C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkynyl or alkylene-cycloalkyl  
radical or an optionally substituted  
C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, aryl, arylalkyl, hetaryl or  
hetarylalkyl radical,

$R_A^{15}$ ,  $R_A^{16}$ ,

are, independently of one another, hydrogen, a  
branched or unbranched, optionally substituted  
C<sub>1</sub>-C<sub>6</sub>-alkyl, CO-C<sub>1</sub>-C<sub>6</sub>-alkyl, SO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub>-alkyl,  
COO-C<sub>1</sub>-C<sub>6</sub>-alkyl, arylalkyl, COO-alkylene-aryl,  
SO<sub>2</sub>-alkylene-aryl or hetarylalkyl radical or an  
optionally substituted C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, aryl,  
CO-aryl, SO<sub>2</sub>-aryl, hetaryl or CO-hetaryl radical,

$R_A^{13}$ ,  $R_A^{14}$

are, independently of one another, hydrogen,  
-(CH<sub>2</sub>)<sub>n</sub>-(X<sub>A</sub>)<sub>j</sub>- $R_A^{12}$ , or the two radicals together are a 3-  
to 8-membered, saturated, unsaturated or aromatic N  
heterocyclic system which may additionally contain two  
other identical or different heteroatoms O, N or S, it  
being possible for the ring optionally to be substituted

or for another, optionally substituted, saturated,  
unsaturated or aromatic ring to be fused onto this ring,

where

- 5
- n can be 0, 1, 2 or 3,
- j can be 0 or 1,
- 10  $X_A$  can be  $-SO_2-$ ,  $-S-$ ,  $-O-$ ,  $-CO-$ ,  $-O-CO-$ ,  $-CO-O-$ ,  
 $-CO-N(R_A^{12})-$ ,  $-N(R_A^{12})-CO-$ ,  $-N(R_A^{12})-SO_2-$  or  
 $-SO_2-N(R_A^{12})-$  and
- 15  $R_A^{12}$  can be hydrogen, a branched or unbranched, optionally  
substituted  $C_1-C_6$ -alkyl,  $C_1-C_4$ -alkoxy,  
 $-O$ -alkylene-aryl or  $-O$ -aryl radical, an amino radical  
with primary or, where appropriate, secondary or  
tertiary substitution, an optionally  $C_1-C_4$ -alkyl- or  
20 aryl-substituted  $C_2-C_6$ -alkynyl or  $C_2-C_6$ -alkenyl  
radical or a 3- to 6-membered, saturated or  
unsaturated heterocyclic system which is substituted  
by up to three identical or different radicals and  
which may contain up to three different or identical  
heteroatoms O, N, S,  $C_3-C_7$ -cycloalkyl, aryl or  
25 hetaryl radical, it being possible for two radicals  
together to be a fused-on, saturated, unsaturated or  
aromatic carbocyclic or heterocyclic system which may  
contain up to three different or identical  
heteroatoms O, N, S, and the ring may optionally be  
30 substituted, or another, optionally substituted,  
saturated, unsaturated or aromatic ring may be fused  
onto this ring,
- $R_A^5$  is a branched or unbranched, optionally substituted  
35  $C_1-C_6$ -alkyl, arylalkyl,  $C_3-C_7$ -cycloalkyl or  
 $C_1-C_6$ -alkyl- $C_3-C_7$ -cycloalkyl radical or an optionally  
substituted aryl radical,
- 40  $R_A^6$ ,  $R_A^{6*}$   
are hydrogen, a branched or unbranched, optionally  
substituted  $C_1-C_4$ -alkyl,  $-CO-O-C_1-C_4$ -alkyl, arylalkyl,  
 $-CO-O$ -alkylene-aryl,  $-CO-O$ -allyl,  $-CO-C_1-C_4$ -alkyl,  
 $-CO$ -alkylene-aryl,  $C_3-C_7$ -cycloalkyl or  $-CO$ -allyl radical  
or the two radicals  $R_A^6$  and  $R_A^{6*}$  in the structural element  
45  $I_A^7$  together are an optionally substituted, saturated,  
unsaturated or aromatic heterocyclic system which may, in

addition to the ring nitrogen, contain up to two further different or identical heteroatoms O, N, S,

- 5  $R_A^7$  is hydrogen, -OH, -CN, -CONH<sub>2</sub>, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl or -O-CO-C<sub>1</sub>-C<sub>4</sub>-alkyl radical, or an optionally substituted arylalkyl, -O-alkylene-aryl, -O-CO-aryl, -O-CO-alkylene-aryl or -O-CO-allyl radical, or the two radicals  $R_A^6$  and  $R_A^7$  together are an optionally substituted, unsaturated or aromatic heterocyclic system which may, in addition to the ring nitrogen, contain up to two further different or identical heteroatoms O, N, S,
- 10
- 15  $R_A^8$  is hydrogen, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>4</sub>-alkyl, CO-C<sub>1</sub>-C<sub>4</sub>-alkyl, SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub>-alkyl or CO-O-C<sub>1</sub>-C<sub>4</sub>-alkyl radical or an optionally substituted aryl, CO-aryl, SO<sub>2</sub>-aryl, CO-O-aryl, CO-alkylene-aryl, SO<sub>2</sub>-alkylene-aryl, CO-O-alkylene-aryl or alkylene-aryl radical,
- 20
- $R_A^9$ ,  $R_A^{10}$  are, independently of one another, hydrogen, -CN, halogen, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl radical or an optionally substituted aryl, arylalkyl, hetaryl, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl radical or a CO-O- $R_A^{14}$ , O- $R_A^{14}$ , S- $R_A^{14}$ , NR<sub>A</sub><sup>15</sup> $R_A^{16}$  or CO-NR<sub>A</sub><sup>15</sup> $R_A^{16}$  radical, or the two  $R_A^9$  and  $R_A^{10}$  radicals in the structural element I<sub>A</sub><sup>14</sup> together are a 5- to 7-membered saturated, unsaturated or aromatic carbocyclic or heterocyclic system which may contain up to three different or identical heteroatoms O, N, S and is optionally substituted by up to three identical or different radicals,
- 25
- 30
- 35  $R_A^{11}$  is hydrogen, -CN, halogen, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl radical or an optionally substituted aryl, arylalkyl, hetaryl, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl radical or a CO-O- $R_A^{14}$ , O- $R_A^{14}$ , S- $R_A^{14}$ , NR<sub>A</sub><sup>15</sup> $R_A^{16}$  or CO-NR<sub>A</sub><sup>15</sup> $R_A^{16}$  radical,
- 40
- $R_A^{17}$  in the structural element I<sub>A</sub><sup>16</sup> the two radicals  $R_A^9$  and  $R_A^{17}$  together are a 5- to 7-membered saturated, unsaturated or aromatic heterocyclic system which may, in addition to the ring nitrogen, contain up to three different or identical heteroatoms O, N, S, and is
- 45

optionally substituted by up to three identical or different radicals,

$Z^1, Z^2, Z^3, Z^4$

are, independently of one another, nitrogen, C-H, C-halogen or a branched or unbranched, optionally substituted C-C<sub>1</sub>-C<sub>4</sub>-alkyl or C-C<sub>1</sub>-C<sub>4</sub>-alkoxy radical,

$Z^5$  is  $NR_A^8$ , oxygen or sulfur.

10

4. A compound as claimed in claim 1, wherein the spacer structural element E is composed of two to four partial structural elements selected from the group of  $E^1$  and  $E^2$ , the partial structural elements being linked in any sequence, and  $E^1$  and  $E^2$  having the following meanings:

15

$E^1$  a partial structural element of the formula  $I_{E1}$

$-(X_E)_i-(CH_2)_c-CR_E^1R_E^2-(CH_2)_d-(Y_E)_l-$   $I_{E1}$

20

and

$E^2$  a partial structural element of the formula  $I_{E2}$

25

$-(NR_E^3)_e-(CR_E^4R_E^5)_f-(Q_E)_k-(CR_E^6R_E^7)_g-(NR_E^8)_h-$   $I_{E2}$ ,

where

c, d, f, g

30

are, independently of one another, 0, 1 or 2,

e, h, i, k, l,

are, independently of one another, 0 or 1,

35

$X_E, Q_E$

are, independently of one another, CO, CO- $NR_E^9$ , S, SO, SO<sub>2</sub>, SO<sub>2</sub>- $NR_E^9$ , CS, CS- $NR_E^9$ , CS-O, CO-O, O-CO, O, ethynyl,  $CR_E^{10}$ -O- $CR_E^{11}$ ,  $CR_E^{10}R_E^{11}$ , C(= $CR_E^{10}R_E^{11}$ ),  $CR_E^{10}=CR_E^{11}$ ,  $CR_E^{10}(OR_E^{12})-CR_E^{11}$ ,  $CR_E^{10}-CR_E^{11}(OR_E^{12})$  or an optionally substituted 4- to 11-membered mono- or polycyclic aliphatic or aromatic hydrocarbon which may contain up to 6 double bonds and up to 6 heteroatoms selected from the group of N, O, S,

40

45

$Y_E$  is -CO-, - $NR_E^9$ -CO-, -SO-, -SO<sub>2</sub>-, - $NR_E^9$ -SO<sub>2</sub>-, -CS-, - $NR_E^9$ -CS-, -O-CS- or -O-CO-

$$R_E^1, R_E^2, R_E^4, R_E^5, R_E^6, R_E^7$$

are, independently of one another, hydrogen, halogen, a hydroxyl group, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkynyl or alkylene-cycloalkyl radical, a -(CH<sub>2</sub>)<sub>w</sub>-R<sub>E</sub><sup>13</sup> radical, an optionally substituted C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, aryl, arylalkyl, hetaryl, hetarylalkyl, O-aryl or O-alkylene-aryl radical, or, independently of one another, in each case two radicals R<sub>E</sub><sup>1</sup> and R<sub>E</sub><sup>2</sup> or R<sub>E</sub><sup>4</sup> and R<sub>E</sub><sup>5</sup> or R<sub>E</sub><sup>6</sup> and R<sub>E</sub><sup>7</sup> together are a 3- to 7-membered, optionally substituted, saturated or unsaturated carbocyclic system,

where

w is 0, 1, 2, 3 or 4,

 $R_E^3, R_E^8, R_E^9$ 

are, independently of one another, hydrogen, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl, CO-C<sub>1</sub>-C<sub>6</sub>-alkyl, CO-O-C<sub>1</sub>-C<sub>6</sub>-alkyl or SO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub>-alkyl radical or an optionally substituted C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, CO-O-alkylene-aryl, CO-alkylene-aryl, CO-aryl, SO<sub>2</sub>-aryl, CO-hetaryl or SO<sub>2</sub>-alkylene-aryl radical,

 $R_E^{10}, R_E^{11}$ 

are, independently of one another, hydrogen, a hydroxyl group, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkynyl or alkylene-cycloalkyl radical or an optionally substituted C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, aryl, arylalkyl, hetaryl or hetarylalkyl radical,

R<sub>E</sub><sup>12</sup> is hydrogen, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkynyl or alkylene-cycloalkyl radical or an optionally substituted C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, aryl, arylalkyl, hetaryl or hetarylalkyl radical,

R<sub>E</sub><sup>13</sup> is hydrogen, a hydroxyl group, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, -arylalkyl, -O-alkylene-aryl or -O-aryl radical, an amino radical with primary or, where appropriate, secondary or tertiary substitution, an optionally C<sub>1</sub>-C<sub>4</sub>-alkyl- or aryl-substituted

5 C<sub>2</sub>-C<sub>6</sub>-alkynyl or C<sub>2</sub>-C<sub>6</sub>-alkenyl radical, a  
 C<sub>5</sub>-C<sub>12</sub>-bicycloalkyl, C<sub>6</sub>-C<sub>18</sub>-tricycloalkyl radical, a  
 CO-O-R<sub>A</sub><sup>14</sup> radical, or a 3- to 6-membered, saturated  
 or unsaturated heterocyclic system which is  
 10 substituted by up to three identical or different  
 radicals and which may contain up to three different  
 or identical heteroatoms O, N, S,  
 C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, aryl or hetaryl radical, it being  
 possible for two radicals together to be a fused-on,  
 saturated, unsaturated or aromatic carbocyclic or  
 heterocyclic system which may contain up to three  
 15 different or identical heteroatoms O, N, S, and the  
 ring may optionally be substituted or another,  
 optionally substituted, saturated, unsaturated or  
 aromatic ring may be fused onto this ring.

5. A compound as claimed in claim , wherein the  
 spacer structural element E used is a structural element of  
 the formula I<sub>E1E2</sub>

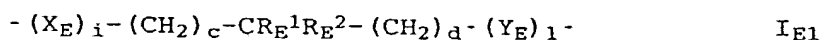
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and E<sup>1</sup> and E<sup>2</sup> have the following meanings:

25

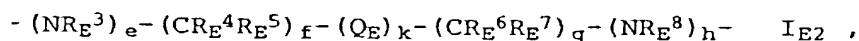
E<sup>1</sup> a partial structural element of the formula I<sub>E1</sub>



and

30

E<sup>2</sup> a partial structural element of the formula I<sub>E2</sub>



35

where

c, d, f, g

are, independently of one another, 0, 1 or 2,

40

e, h, i, k, l

are, independently of one another, 0 or 1,

X<sub>E</sub>, Q<sub>E</sub>

45

are, independently of one another, CO, CO-NR<sub>E</sub><sup>9</sup>, S,  
 SO, SO<sub>2</sub>, SO<sub>2</sub>NR<sub>E</sub><sup>9</sup>, CS, CS-NR<sub>E</sub><sup>9</sup>, CS-O, CO-O, O-CO, O,  
 ethynyl, CR<sub>E</sub><sup>10</sup>-O-CR<sub>E</sub><sup>11</sup>, CR<sub>E</sub><sup>10</sup>R<sub>E</sub><sup>11</sup>, C(=CR<sub>E</sub><sup>10</sup>R<sub>E</sub><sup>11</sup>),  
 CR<sub>E</sub><sup>10</sup>=CR<sub>E</sub><sup>11</sup>, CR<sub>E</sub><sup>10</sup>(OR<sub>E</sub><sup>12</sup>)-CR<sub>E</sub><sup>11</sup>, CR<sub>E</sub><sup>10</sup>-CR<sub>E</sub><sup>11</sup>(OR<sub>E</sub><sup>12</sup>) or an

optionally substituted 4- to 11-membered mono- or polycyclic aliphatic or aromatic hydrocarbon which may contain up to 6 double bonds and up to 6 heteroatoms selected from the group of N, O, S,

5

$Y_E$  is  $-CO-$ ,  $-NR_E^9-CO-$ ,  $-SO-$ ,  $-SO_2-$ ,  $-NR_E^9-SO_2-$ ,  $-CS-$ ,  $-NR_E^9-CS-$ ,  $-O-CS-$  or  $-O-CO-$

10

$R_E^1$ ,  $R_E^2$ ,  $R_E^4$ ,  $R_E^5$ ,  $R_E^6$ ,  $R_E^7$

are, independently of one another, hydrogen, halogen, a hydroxyl group, a branched or unbranched, optionally substituted  $C_1-C_6$ -alkyl,  $C_1-C_4$ -alkoxy,  $C_2-C_6$ -alkenyl,  $C_2-C_6$ -alkynyl or alkylene-cycloalkyl radical, a  $-(CH_2)_w-R_E^{13}$  radical, an optionally substituted  $C_3-C_7$ -cycloalkyl, aryl, arylalkyl, hetaryl, hetarylalkyl, O-aryl or O-alkylene-aryl radical, or, independently of one another, in each case two radicals  $R_E^1$  and  $R_E^2$  or  $R_E^4$  and  $R_E^5$  or  $R_E^6$  and  $R_E^7$  together are a 3- to 7-membered, optionally substituted, saturated or unsaturated carbocyclic system,

15

20

where

25

w is 0, 1, 2, 3 or 4,

30

$R_E^3$ ,  $R_E^8$ ,  $R_E^9$

are, independently of one another, hydrogen, a branched or unbranched, optionally substituted  $C_1-C_6$ -alkyl,  $CO-C_1-C_6$ -alkyl,  $CO-O-C_1-C_6$ -alkyl or  $SO_2-C_1-C_6$ -alkyl radical or an optionally substituted  $C_3-C_7$ -cycloalkyl,  $CO-O$ -alkylene-aryl,  $CO$ -alkylene-aryl,  $CO$ -aryl,  $SO_2$ -aryl,  $CO$ -hetaryl or  $SO_2$ -alkylene-aryl radical,

35

$R_E^{10}$ ,  $R_E^{11}$

are, independently of one another, hydrogen, a hydroxyl group, a branched or unbranched, optionally substituted  $C_1-C_6$ -alkyl,  $C_1-C_4$ -alkoxy,  $C_2-C_6$ -alkenyl,  $C_2-C_6$ -alkynyl or alkylene-cycloalkyl radical or an optionally substituted  $C_3-C_7$ -cycloalkyl, aryl, arylalkyl, hetaryl or hetarylalkyl radical,

40

45

$R_E^{12}$  is hydrogen, a branched or unbranched, optionally substituted  $C_1-C_6$ -alkyl,  $C_2-C_6$ -alkenyl,  $C_2-C_6$ -alkynyl or alkylene-cycloalkyl radical or an optionally

substituted C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, aryl, arylalkyl, hetaryl or hetarylalkyl radical,

5 R<sub>E</sub><sup>13</sup> is hydrogen, a hydroxyl group, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, arylalkyl, -O-alkylene-aryl or -O-aryl radical, an amino radical with primary or, where appropriate, secondary or tertiary substitution, an optionally C<sub>1</sub>-C<sub>4</sub>-alkyl- or aryl-substituted 10 C<sub>2</sub>-C<sub>6</sub>-alkynyl or C<sub>2</sub>-C<sub>6</sub>-alkenyl radical, a C<sub>5</sub>-C<sub>12</sub>-bicycloalkyl, C<sub>6</sub>-C<sub>18</sub>-tricycloalkyl radical, a CO-O-R<sub>A</sub><sup>14</sup> radical, or a 3- to 6-membered, saturated or unsaturated heterocyclic system which is substituted by up to three identical or different 15 radicals and which may contain up to three different or identical heteroatoms O, N, S, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, aryl or hetaryl radical, it being possible for two radicals together to be a fused-on, saturated, unsaturated or aromatic carbocyclic or heterocyclic 20 system which may contain up to three different or identical heteroatoms O, N, S, and the ring may optionally be substituted, or another, optionally substituted, saturated, unsaturated or aromatic ring may be fused onto this ring.

6. A process for preparing compounds which bind to integrin receptors, said process comprising using a structural element of the formula I<sub>GL</sub>



35 L a structural element of the formula I<sub>L</sub>



where

40 T is a COOH group or a radical which can be hydrolyzed to COOH and

-U- is -(X<sub>L</sub>)<sub>a</sub>-(CR<sub>L</sub><sup>1</sup>R<sub>L</sub><sup>2</sup>)<sub>b</sub>-, -CR<sub>L</sub><sup>1</sup>=CR<sub>L</sub><sup>2</sup>-, ethynylene or =CR<sub>L</sub><sup>1</sup>-, where

45 a is 0 or 1,



$X_L$  is  $CR_L^3R_L^4$ ,  $NR_L^5$ , oxygen or sulfur,

$$5 \quad R_L^1, R_L^2, R_L^3, R_L^4$$

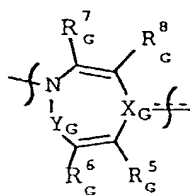
are, independently of one another, hydrogen, -T, -OH, -NR<sub>L</sub><sup>6</sup>R<sub>L</sub><sup>7</sup>, -CO-NH<sub>2</sub>, a halogen radical, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkynyl, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, -CO-NH(C<sub>1</sub>-C<sub>6</sub>-alkyl), -CO-N(C<sub>1</sub>-C<sub>6</sub>-alkyl)<sub>2</sub> or C<sub>1</sub>-C<sub>4</sub>-alkoxy radical, an optionally substituted C<sub>1</sub>-C<sub>2</sub>-alkylene-T, C<sub>2</sub>-alkenylene-T or C<sub>2</sub>-alkynylene-T radical or, in each case independently of one another, two radicals R<sub>L</sub><sup>1</sup> and R<sub>L</sub><sup>2</sup> or R<sub>L</sub><sup>3</sup> and R<sub>L</sub><sup>4</sup> or, where appropriate, R<sub>L</sub><sup>1</sup> and R<sub>L</sub><sup>3</sup> together are an optionally substituted 3- to 7-membered saturated or unsaturated carbocyclic or heterocyclic system which may contain up to three different or identical heteroatoms O, N, S,

 $R_L^5, R_L^6, R_L^7$ 

are, independently of one another, hydrogen, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, CO-O-C<sub>1</sub>-C<sub>6</sub>-alkyl, SO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub>-alkyl or CO-C<sub>1</sub>-C<sub>6</sub>-alkyl radical or an optionally substituted CO-O-alkylene-aryl, SO<sub>2</sub>-aryl, CO-aryl, SO<sub>2</sub>-alkylene-aryl or CO-alkylene-aryl radical.

30

G a structural element of the formula I<sub>G</sub>

 $I_G$ 

40

where

the structural element G can be incorporated in both orientations, and

45

$X_G$  is nitrogen or  $CR_G^1$  in the case where structural element G is connected to structural element L or B via  $X_G$  by a single bond,

or

carbon in the case where structural element G is  
connected to structural element L via  $X_G$  by a double  
bond,

$Y_G$  is CO, CS,  $C=NR_G^2$  or  $CR_G^3R_G^4$ ,

where

$R_G^1$  is hydrogen, halogen, a hydroxyl group or a branched  
or unbranched, optionally substituted  $C_1$ - $C_6$ -alkyl or  
 $C_1$ - $C_4$ -alkoxy radical,

$R_G^2$  is hydrogen, a hydroxyl group, a branched or  
unbranched, optionally substituted  $C_1$ - $C_6$ -alkyl,  
 $C_1$ - $C_4$ -alkoxy,  $C_3$ - $C_7$ -cycloalkyl or -O- $C_3$ - $C_7$ -cycloalkyl  
radical or an optionally substituted aryl, -O-aryl,  
arylalkyl or -O-alkylene-aryl radical and

$R_G^3$ ,  $R_G^4$   
are, independently of one another, hydrogen or a  
branched or unbranched, optionally substituted  
 $C_1$ - $C_6$ -alkyl,  $C_2$ - $C_6$ -alkenyl,  $C_2$ - $C_6$ -alkynyl or  
 $C_1$ - $C_4$ -alkoxy radical or the two  $R_G^3$  and  $R_G^4$  radicals  
together are a cyclic acetal -O-CH<sub>2</sub>-CH<sub>2</sub>-O- or  
-O-CH<sub>2</sub>-O- or the two  $R_G^3$  and  $R_G^4$  radicals together are  
an optionally substituted  $C_3$ - $C_7$ -cycloalkyl radical,

$R_G^5$ ,  $R_G^6$ ,  $R_G^7$ ,  $R_G^8$

are, independently of one another, hydrogen, an amino or  
hydroxyl group, an HN-CO- $R_G^9$  radical, a branched or  
unbranched, optionally substituted  $C_1$ - $C_6$ -alkyl or  
 $C_1$ - $C_4$ -alkoxy radical, an optionally substituted aryl or  
arylalkyl radical or, independently of one another, in  
each case two  $R_G^5$  and  $R_G^6$  or  $R_G^7$  and  $R_G^8$  radicals together  
are an optionally substituted, fused-on, unsaturated or  
aromatic 3- to 6-membered carbocyclic or heterocyclic  
system which may contain up to three different or  
identical heteroatoms O, N, S, and

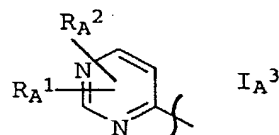
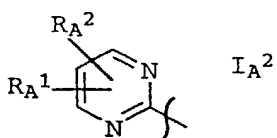
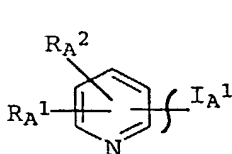
$R_G^9$  is a branched or unbranched, optionally substituted  
 $C_1$ - $C_6$ -alkyl or  $C_1$ - $C_4$ -alkoxy radical or an optionally  
substituted aryl, hetaryl, arylalkyl or hetarylalkyl  
radical.

8. A pharmaceutical preparation for oral or parenteral use, comprising at least one compound as claimed in claim 1 in addition to conventional pharmaceutical excipients
12. A process for the treatment of diseases in which the interaction between integrins and their natural ligands is excessive, said process comprising administering an effective amount of a drug produced from the compound of claim 1 to a mammal.
13. The process as claimed in claim 12 wherein the disease is one in which the interaction between  $\text{A}_\alpha\beta_3$  integrin and its natural ligands is excessive.
14. The process as claimed in claim 13 wherein the disease is atherosclerosis, restenosis after vessel injury, angioplasty, acute kidney failure, angiogenesis-associated microangiopathies, arterial thrombosis, stroke, angiogenesis, tumor growth and metastasis, cancer, osteoporosis, high blood pressure, psoriasis or viral, parasitic or bacterial diseases, inflammations, hyperparathyroidism, Paget's disease, malignant hypercalcemia or metastatic osteolytic lesions.

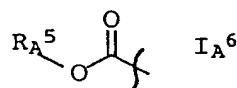
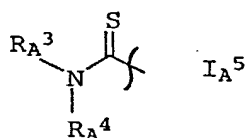
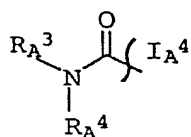
3. A compound as claimed in claim 1 [either of claims 1 or 2], wherein the structural element used as structural element A is selected from the group of structural elements of the formulae I<sub>A</sub><sup>1</sup> to I<sub>A</sub><sup>18</sup>,

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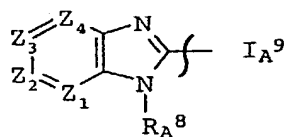
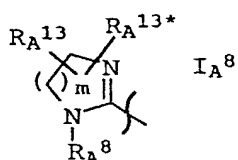
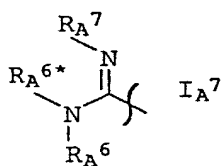
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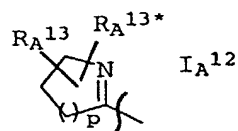
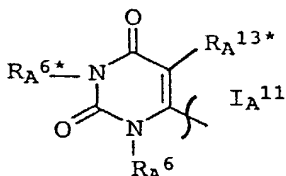
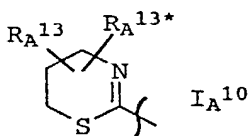
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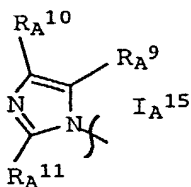
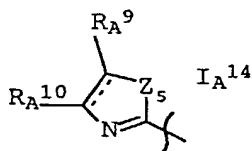
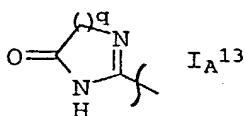
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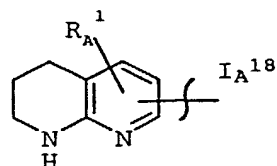
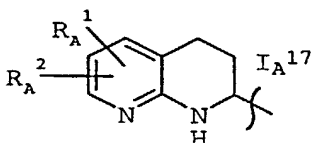
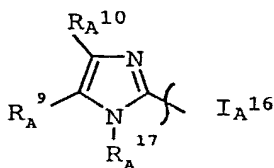
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30



35



40

where

m, p, q

are, independently of one another, 1, 2 or 3,

45

$R_A^1, R_A^2$

are, independently of one another, hydrogen, CN, halogen,  
 a branched or unbranched, optionally substituted  
 $C_1$ - $C_6$ -alkyl or CO- $C_1$ - $C_6$ -alkyl radical or an optionally  
 substituted aryl, arylalkyl, hetaryl, hetarylalkyl or  
 $C_3$ - $C_7$ -cycloalkyl radical or a radical CO-O- $R_A^{14}$ , O- $R_A^{14}$ ,  
 $S$ - $R_A^{14}$ ,  $NR_A^{15}R_A^{16}$ , CO- $NR_A^{15}R_A^{16}$  or  $SO_2NR_A^{15}R_A^{16}$  or the two  $R_A^1$   
 and  $R_A^2$  radicals together are a fused-on, optionally  
 substituted 5- or 6-membered, unsaturated or aromatic  
 carbocyclic or heterocyclic system which may contain up  
 to three heteroatoms selected from the group of O, N, or  
 S,

$R_A^{13}, R_A^{13*}$

are, independently of one another, hydrogen, CN, halogen,  
 a branched or unbranched, optionally substituted  
 $C_1$ - $C_6$ -alkyl radical or an optionally substituted aryl,  
 arylalkyl, hetaryl,  $C_3$ - $C_7$ -cycloalkyl radical or a  
 CO-O- $R_A^{14}$ , O- $R_A^{14}$ ,  $S$ - $R_A^{14}$ ,  $NR_A^{15}R_A^{16}$  or CO- $NR_A^{15}R_A^{16}$  radical,  
 where

$R_A^{14}$  is hydrogen, a branched or unbranched, optionally  
 substituted  $C_1$ - $C_6$ -alkyl, alkylene- $C_1$ - $C_4$ -alkoxy,  
 $C_2$ - $C_6$ -alkenyl,  $C_2$ - $C_6$ -alkynyl or alkylene-cycloalkyl  
 radical or an optionally substituted  
 $C_3$ - $C_7$ -cycloalkyl, aryl, arylalkyl, hetaryl or  
 hetarylalkyl radical,

$R_A^{15}, R_A^{16},$

are, independently of one another, hydrogen, a  
 branched or unbranched, optionally substituted  
 $C_1$ - $C_6$ -alkyl, CO- $C_1$ - $C_6$ -alkyl,  $SO_2$ - $C_1$ - $C_6$ -alkyl,  
 COO- $C_1$ - $C_6$ -alkyl, arylalkyl, COO-alkylene-aryl,  
 $SO_2$ -alkylene-aryl or hetarylalkyl radical or an  
 optionally substituted  $C_3$ - $C_7$ -cycloalkyl, aryl,  
 CO-aryl,  $SO_2$ -aryl, hetaryl or CO-hetaryl radical,

$R_A^3, R_A^4$

are, independently of one another, hydrogen,  
 $-(CH_2)_n-(X_A)_j-R_A^{12}$ , or the two radicals together are a 3-  
 to 8-membered, saturated, unsaturated or aromatic N  
 heterocyclic system which may additionally contain two  
 other identical or different heteroatoms O, N or S, it  
 being possible for the ring optionally to be substituted

or for another, optionally substituted, saturated, unsaturated or aromatic ring to be fused onto this ring,

where

- 5
- n can be 0, 1, 2 or 3,
- j can be 0 or 1,
- 10  $X_A$  can be  $-SO_2-$ ,  $-S-$ ,  $-O-$ ,  $-CO-$ ,  $-O-CO-$ ,  $-CO-O-$ ,  $-CO-N(R_A^{12})-$ ,  $-N(R_A^{12})-CO-$ ,  $-N(R_A^{12})-SO_2-$  or  $-SO_2-N(R_A^{12})-$  and
- 15  $R_A^{12}$  can be hydrogen, a branched or unbranched, optionally substituted  $C_1-C_6$ -alkyl,  $C_1-C_4$ -alkoxy,  $-O$ -alkylene-aryl or  $-O$ -aryl radical, an amino radical with primary or, where appropriate, secondary or tertiary substitution, an optionally  $C_1-C_4$ -alkyl- or aryl-substituted  $C_2-C_6$ -alkynyl or  $C_2-C_6$ -alkenyl
- 20 radical or a 3- to 6-membered, saturated or unsaturated heterocyclic system which is substituted by up to three identical or different radicals and which may contain up to three different or identical heteroatoms O, N, S,  $C_3-C_7$ -cycloalkyl, aryl or
- 25 hetaryl radical, it being possible for two radicals together to be a fused-on, saturated, unsaturated or aromatic carbocyclic or heterocyclic system which may contain up to three different or identical
- 30 heteroatoms O, N, S, and the ring may optionally be substituted, or another, optionally substituted, saturated, unsaturated or aromatic ring may be fused onto this ring,
- 35  $R_A^5$  is a branched or unbranched, optionally substituted  $C_1-C_6$ -alkyl, arylalkyl,  $C_3-C_7$ -cycloalkyl or  $C_1-C_6$ -alkyl- $C_3-C_7$ -cycloalkyl radical or an optionally substituted aryl radical,
- 40  $R_A^6$ ,  $R_A^{6*}$  are hydrogen, a branched or unbranched, optionally substituted  $C_1-C_4$ -alkyl,  $-CO-O-C_1-C_4$ -alkyl, arylalkyl,  $-CO-O$ -alkylene-aryl,  $-CO-O$ -allyl,  $-CO-C_1-C_4$ -alkyl,  $-CO$ -alkylene-aryl,  $C_3-C_7$ -cycloalkyl or  $-CO$ -allyl radical
- 45 or the two radicals  $R_A^6$  and  $R_A^{6*}$  in the structural element  $I_A^7$  together are an optionally substituted, saturated, unsaturated or aromatic heterocyclic system which may, in

addition to the ring nitrogen, contain up to two further different or identical heteroatoms O, N, S,

5  $R_A^7$  is hydrogen, -OH, -CN, -CONH<sub>2</sub>, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl or -O-CO-C<sub>1</sub>-C<sub>4</sub>-alkyl radical, or an optionally substituted arylalkyl, -O-alkylene-aryl, -O-CO-aryl, -O-CO-alkylene-aryl or -O-CO-allyl radical, 10 or the two radicals  $R_A^6$  and  $R_A^7$  together are an optionally substituted, unsaturated or aromatic heterocyclic system which may, in addition to the ring nitrogen, contain up to two further different or identical heteroatoms O, N, S,

15  $R_A^8$  is hydrogen, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>4</sub>-alkyl, CO-C<sub>1</sub>-C<sub>4</sub>-alkyl, SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub>-alkyl or CO-O-C<sub>1</sub>-C<sub>4</sub>-alkyl radical or an optionally substituted aryl, CO-aryl, SO<sub>2</sub>-aryl, CO-O-aryl, CO-alkylene-aryl, 20 SO<sub>2</sub>-alkylene-aryl, CO-O-alkylene-aryl or alkylene-aryl radical,

$R_A^9$ ,  $R_A^{10}$  are, independently of one another, hydrogen, -CN, halogen, a branched or unbranched, optionally substituted 25 C<sub>1</sub>-C<sub>6</sub>-alkyl radical or an optionally substituted aryl, arylalkyl, hetaryl, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl radical or a CO-O- $R_A^{14}$ , O- $R_A^{14}$ , S- $R_A^{14}$ , NR<sub>A</sub><sup>15</sup> $R_A^{16}$  or CO-NR<sub>A</sub><sup>15</sup> $R_A^{16}$  radical, or the two  $R_A^9$  and  $R_A^{10}$  radicals in the structural element I<sub>A</sub><sup>14</sup> together are a 5- to 7-membered saturated, 30 unsaturated or aromatic carbocyclic or heterocyclic system which may contain up to three different or identical heteroatoms O, N, S and is optionally substituted by up to three identical or different radicals,

35  $R_A^{11}$  is hydrogen, -CN, halogen, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl radical or an optionally substituted aryl, arylalkyl, hetaryl, 40 C<sub>3</sub>-C<sub>7</sub>-cycloalkyl radical or a CO-O- $R_A^{14}$ , O- $R_A^{14}$ , S- $R_A^{14}$ , NR<sub>A</sub><sup>15</sup> $R_A^{16}$  or CO-NR<sub>A</sub><sup>15</sup> $R_A^{16}$  radical,

$R_A^{17}$  in the structural element I<sub>A</sub><sup>16</sup> the two radicals  $R_A^9$  and  $R_A^{17}$  together are a 5- to 7-membered saturated, 45 unsaturated or aromatic heterocyclic system which may, in addition to the ring nitrogen, contain up to three different or identical heteroatoms O, N, S, and is

optionally substituted by up to three identical or different radicals,

$Z^1, Z^2, Z^3, Z^4$

are, independently of one another, nitrogen, C-H, C-halogen or a branched or unbranched, optionally substituted C-C<sub>1</sub>-C<sub>4</sub>-alkyl or C-C<sub>1</sub>-C<sub>4</sub>-alkoxy radical,

$Z^5$  is  $NR_A^8$ , oxygen or sulfur.

10

4. A compound as claimed in claim 1 [any of claims 1 to 3], wherein the spacer structural element E is composed of two to four partial structural elements selected from the group of  $E^1$  and  $E^2$ , the partial structural elements being linked in any sequence, and  $E^1$  and  $E^2$  having the following meanings:

15

$E^1$  a partial structural element of the formula  $I_{E1}$

$-(X_E)_i-(CH_2)_c-CR_E^1R_E^2-(CH_2)_d-(Y_E)_l-$   $I_{E1}$

20

and

$E^2$  a partial structural element of the formula  $I_{E2}$

25

$-(NR_E^3)_e-(CR_E^4R_E^5)_f-(Q_E)_k-(CR_E^6R_E^7)_g-(NR_E^8)_h-$   $I_{E2}$ ,

where

$c, d, f, g$

30

are, independently of one another, 0, 1 or 2,

$e, h, i, k, l,$

are, independently of one another, 0 or 1,

35

$X_E, Q_E$

are, independently of one another, CO, CO- $NR_E^9$ , S, SO, SO<sub>2</sub>, SO<sub>2</sub> $NR_E^9$ , CS, CS- $NR_E^9$ , CS-O, CO-O, O-CO, O, ethynyl,  $CR_E^{10}$ -O- $CR_E^{11}$ ,  $CR_E^{10}R_E^{11}$ ,  $C(=CR_E^{10}R_E^{11})$ ,  $CR_E^{10}=CR_E^{11}$ ,  $CR_E^{10}(OR_E^{12})-CR_E^{11}$ ,  $CR_E^{10}-CR_E^{11}(OR_E^{12})$  or an optionally substituted 4- to 11-membered mono- or polycyclic aliphatic or aromatic hydrocarbon which may contain up to 6 double bonds and up to 6 heteroatoms selected from the group of N, O, S,

40

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$Y_E$  is -CO-, - $NR_E^9$ -CO-, -SO-, -SO<sub>2</sub>-, - $NR_E^9$ -SO<sub>2</sub>-, -CS-, - $NR_E^9$ -CS-, -O-CS- or -O-CO-



$R_E^1, R_E^2, R_E^4, R_E^5, R_E^6, R_E^7$

are, independently of one another, hydrogen, halogen, a hydroxyl group, a branched or unbranched, optionally substituted  $C_1-C_6$ -alkyl,  $C_1-C_4$ -alkoxy,  $C_2-C_6$ -alkenyl,  $C_2-C_6$ -alkynyl or alkylene-cycloalkyl radical, a  $-(CH_2)_w-R_E^{13}$  radical, an optionally substituted  $C_3-C_7$ -cycloalkyl, aryl, arylalkyl, hetaryl, hetarylalkyl, O-aryl or O-alkylene-aryl radical, or, independently of one another, in each case two radicals  $R_E^1$  and  $R_E^2$  or  $R_E^4$  and  $R_E^5$  or  $R_E^6$  and  $R_E^7$  together are a 3- to 7-membered, optionally substituted, saturated or unsaturated carbocyclic system,

where

$w$  is 0, 1, 2, 3 or 4,

$R_E^3, R_E^8, R_E^9$

are, independently of one another, hydrogen, a branched or unbranched, optionally substituted  $C_1-C_6$ -alkyl, CO- $C_1-C_6$ -alkyl, CO-O- $C_1-C_6$ -alkyl or SO<sub>2</sub>- $C_1-C_6$ -alkyl radical or an optionally substituted  $C_3-C_7$ -cycloalkyl, CO-O-alkylene-aryl, CO-alkylene-aryl, CO-aryl, SO<sub>2</sub>-aryl, CO-hetaryl or SO<sub>2</sub>-alkylene-aryl radical,

$R_E^{10}, R_E^{11}$

are, independently of one another, hydrogen, a hydroxyl group, a branched or unbranched, optionally substituted  $C_1-C_6$ -alkyl,  $C_1-C_4$ -alkoxy,  $C_2-C_6$ -alkenyl,  $C_2-C_6$ -alkynyl or alkylene-cycloalkyl radical or an optionally substituted  $C_3-C_7$ -cycloalkyl, aryl, arylalkyl, arylalkyl, hetaryl or hetarylalkyl radical,

$R_E^{12}$  is hydrogen, a branched or unbranched, optionally substituted  $C_1-C_6$ -alkyl,  $C_2-C_6$ -alkenyl,  $C_2-C_6$ -alkynyl or alkylene-cycloalkyl radical or an optionally substituted  $C_3-C_7$ -cycloalkyl, aryl, arylalkyl, hetaryl or hetarylalkyl radical,

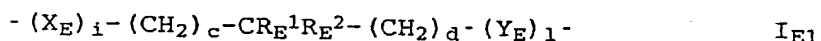
$R_E^{13}$  is hydrogen, a hydroxyl group, a branched or unbranched, optionally substituted  $C_1-C_6$ -alkyl,  $C_1-C_4$ -alkoxy, -arylalkyl, -O-alkylene-aryl or -O-aryl radical, an amino radical with primary or, where appropriate, secondary or tertiary substitution, an optionally  $C_1-C_4$ -alkyl- or aryl-substituted

5. A compound as claimed in claim 1 [any of claims 1 to 4], wherein the spacer structural element E used is a structural element of the formula I<sub>E1E2</sub>



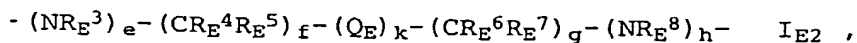
and  $E^1$  and  $E^2$  have the following meanings:

E<sup>1</sup> a partial structural element of the formula I<sub>E1</sub>



and

E<sup>2</sup> a partial structural element of the formula I<sub>E2</sub>



where

c, d, f, g

are, independently of one another, 0, 1 or 2,

e, h, i, k, l

are, independently of one another, 0 or 1,

 $X_E, Q_E$ 

are, independently of one another, CO, CO-NR<sub>E</sub><sup>9</sup>, S, SO, SO<sub>2</sub>, SO<sub>2</sub>NR<sub>E</sub><sup>9</sup>, CS, CS-NR<sub>E</sub><sup>9</sup>, CS-O, CO-O, O-CO, O, ethynyl, CR<sub>E</sub><sup>10</sup>-O-CR<sub>E</sub><sup>11</sup>, CR<sub>E</sub><sup>10</sup>R<sub>E</sub><sup>11</sup>, C(=CR<sub>E</sub><sup>10</sup>R<sub>E</sub><sup>11</sup>), CR<sub>E</sub><sup>10</sup>=CR<sub>E</sub><sup>11</sup>, CR<sub>E</sub><sup>10</sup>(OR<sub>E</sub><sup>12</sup>)-CR<sub>E</sub><sup>11</sup>, CR<sub>E</sub><sup>10</sup>-CR<sub>E</sub><sup>11</sup>(OR<sub>E</sub><sup>12</sup>) or an

optionally substituted 4- to 11-membered mono- or polycyclic aliphatic or aromatic hydrocarbon which may contain up to 6 double bonds and up to 6 heteroatoms selected from the group of N, O, S,

$Y_E$  is  $-CO-$ ,  $-NR_E^9-CO-$ ,  $-SO-$ ,  $-SO_2-$ ,  $-NR_E^9-SO_2-$ ,  $-CS-$ ,  $-NR_E^9-CS-$ ,  $-O-CS-$  or  $-O-CO-$

$R_E^1$ ,  $R_E^2$ ,  $R_E^4$ ,  $R_E^5$ ,  $R_E^6$ ,  $R_E^7$

are, independently of one another, hydrogen, halogen, a hydroxyl group, a branched or unbranched, optionally substituted  $C_1-C_6$ -alkyl,  $C_1-C_4$ -alkoxy,  $C_2-C_6$ -alkenyl,  $C_2-C_6$ -alkynyl or alkylene-cycloalkyl radical, a  $-(CH_2)_w-R_E^{13}$  radical, an optionally substituted  $C_3-C_7$ -cycloalkyl, aryl, arylalkyl, hetaryl, hetarylalkyl, O-aryl or O-alkylene-aryl radical, or, independently of one another, in each case two radicals  $R_E^1$  and  $R_E^2$  or  $R_E^4$  and  $R_E^5$  or  $R_E^6$  and  $R_E^7$  together are a 3- to 7-membered, optionally substituted, saturated or unsaturated carbocyclic system,

where

$w$  is 0, 1, 2, 3 or 4,

$R_E^3$ ,  $R_E^8$ ,  $R_E^9$

are, independently of one another, hydrogen, a branched or unbranched, optionally substituted  $C_1-C_6$ -alkyl,  $CO-C_1-C_6$ -alkyl,  $CO-O-C_1-C_6$ -alkyl or  $SO_2-C_1-C_6$ -alkyl radical or an optionally substituted  $C_3-C_7$ -cycloalkyl,  $CO-O$ -alkylene-aryl,  $CO$ -alkylene-aryl,  $CO$ -aryl,  $SO_2$ -aryl,  $CO$ -hetaryl or  $SO_2$ -alkylene-aryl radical,

$R_E^{10}$ ,  $R_E^{11}$

are, independently of one another, hydrogen, a hydroxyl group, a branched or unbranched, optionally substituted  $C_1-C_6$ -alkyl,  $C_1-C_4$ -alkoxy,  $C_2-C_6$ -alkenyl,  $C_2-C_6$ -alkynyl or alkylene-cycloalkyl radical or an optionally substituted  $C_3-C_7$ -cycloalkyl, aryl, arylalkyl, hetaryl or hetarylalkyl radical,

$R_E^{12}$  is hydrogen, a branched or unbranched, optionally substituted  $C_1-C_6$ -alkyl,  $C_2-C_6$ -alkenyl,  $C_2-C_6$ -alkynyl or alkylene-cycloalkyl radical or an optionally

substituted C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, aryl, arylalkyl, hetaryl or hetarylalkyl radical,

R<sub>E</sub><sup>13</sup> is hydrogen, a hydroxyl group, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, arylalkyl, -O-alkylene-aryl or -O-aryl radical, an amino radical with primary or, where appropriate, secondary or tertiary substitution, an optionally C<sub>1</sub>-C<sub>4</sub>-alkyl- or aryl-substituted C<sub>2</sub>-C<sub>6</sub>-alkynyl or C<sub>2</sub>-C<sub>6</sub>-alkenyl radical, a C<sub>5</sub>-C<sub>12</sub>-bicycloalkyl, C<sub>6</sub>-C<sub>18</sub>-tricycloalkyl radical, a CO-O-R<sub>A</sub><sup>14</sup> radical, or a 3- to 6-membered, saturated or unsaturated heterocyclic system which is substituted by up to three identical or different radicals and which may contain up to three different or identical heteroatoms O, N, S, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, aryl or hetaryl radical, it being possible for two radicals together to be a fused-on, saturated, unsaturated or aromatic carbocyclic or heterocyclic system which may contain up to three different or identical heteroatoms O, N, S, and the ring may optionally be substituted, or another, optionally substituted, saturated, unsaturated or aromatic ring may be fused onto this ring.

6. A process for preparing compounds which bind to integrin receptors, said process comprising using a [The use of the] structural element of the formula I<sub>GL</sub>

-G-L

I<sub>GL</sub>

[to prepare compounds which bind to integrin receptors,]

L a structural element of the formula I<sub>L</sub>

-U-T

I<sub>L</sub>

where

T is a COOH group or a radical which can be hydrolyzed to COOH and

-U- is -(X<sub>L</sub>)<sub>a</sub>-(CR<sub>L</sub><sup>1</sup>R<sub>L</sub><sup>2</sup>)<sub>b</sub>-, -CR<sub>L</sub><sup>1</sup>=CR<sub>L</sub><sup>2</sup>-, ethynylene or =CR<sub>L</sub><sup>1</sup>-, where

a is 0 or 1,

b is 0, 1 or 2

$X_L$  is  $CR_L^3R_L^4$ ,  $NR_L^5$ , oxygen or sulfur,

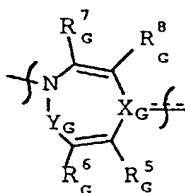
$R_L^1$ ,  $R_L^2$ ,  $R_L^3$ ,  $R_L^4$

are, independently of one another, hydrogen, -T, -OH,  $-NR_L^6R_L^7$ , -CO-NH<sub>2</sub>, a halogen radical, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkynyl, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, -CO-NH(C<sub>1</sub>-C<sub>6</sub>-alkyl), -CO-N(C<sub>1</sub>-C<sub>6</sub>-alkyl)<sub>2</sub> or C<sub>1</sub>-C<sub>4</sub>-alkoxy radical, an optionally substituted C<sub>1</sub>-C<sub>2</sub>-alkylene-T, C<sub>2</sub>-alkenylene-T or C<sub>2</sub>-alkynylene-T radical, an optionally substituted aryl or arylalkyl radical or, in each case independently of one another, two radicals  $R_L^1$  and  $R_L^2$  or  $R_L^3$  and  $R_L^4$  or, where appropriate,  $R_L^1$  and  $R_L^3$  together are an optionally substituted 3- to 7-membered saturated or unsaturated carbocyclic or heterocyclic system which may contain up to three different or identical heteroatoms O, N, S,

$R_L^5$ ,  $R_L^6$ ,  $R_L^7$

are, independently of one another, hydrogen, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, CO-O-C<sub>1</sub>-C<sub>6</sub>-alkyl, SO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub>-alkyl or CO-C<sub>1</sub>-C<sub>6</sub>-alkyl radical or an optionally substituted CO-O-alkylene-aryl, SO<sub>2</sub>-aryl, CO-aryl, SO<sub>2</sub>-alkylene-aryl or CO-alkylene-aryl radical,

G a structural element of the formula I<sub>G</sub>



where

the structural element G can be incorporated in both orientations, and

$X_G$  is nitrogen or  $CR_G^1$  in the case where structural element G is connected to structural element L or B via  $X_G$  by a single bond,

or

carbon in the case where structural element G is  
connected to structural element L via  $X_G$  by a double  
bond,

$Y_G$  is CO, CS,  $C=NR_G^2$  or  $CR_G^3R_G^4$ ,

where

$R_G^1$  is hydrogen, halogen, a hydroxyl group or a branched  
or unbranched, optionally substituted  $C_1$ - $C_6$ -alkyl or  
 $C_1$ - $C_4$ -alkoxy radical,

$R_G^2$  is hydrogen, a hydroxyl group, a branched or  
unbranched, optionally substituted  $C_1$ - $C_6$ -alkyl,  
 $C_1$ - $C_4$ -alkoxy,  $C_3$ - $C_7$ -cycloalkyl or -O- $C_3$ - $C_7$ -cycloalkyl  
radical or an optionally substituted aryl, -O-aryl,  
arylalkyl or -O-alkylene-aryl radical and

$R_G^3$ ,  $R_G^4$   
are, independently of one another, hydrogen or a  
branched or unbranched, optionally substituted  
 $C_1$ - $C_6$ -alkyl,  $C_2$ - $C_6$ -alkenyl,  $C_2$ - $C_6$ -alkynyl or  
 $C_1$ - $C_4$ -alkoxy radical or the two  $R_G^3$  and  $R_G^4$  radicals  
together are a cyclic acetal -O- $CH_2$ - $CH_2$ -O- or  
-O- $CH_2$ -O- or the two  $R_G^3$  and  $R_G^4$  radicals together are  
an optionally substituted  $C_3$ - $C_7$ -cycloalkyl radical,

$R_G^5$ ,  $R_G^6$ ,  $R_G^7$ ,  $R_G^8$

are, independently of one another, hydrogen, an amino or  
hydroxyl group, an HN-CO- $R_G^9$  radical, a branched or  
unbranched, optionally substituted  $C_1$ - $C_6$ -alkyl or  
 $C_1$ - $C_4$ -alkoxy radical, an optionally substituted aryl or  
arylalkyl radical or, independently of one another, in  
each case two  $R_G^5$  and  $R_G^6$  or  $R_G^7$  and  $R_G^8$  radicals together  
are an optionally substituted, fused-on, unsaturated or  
aromatic 3- to 6-membered carbocyclic or heterocyclic  
system which may contain up to three different or  
identical heteroatoms O, N, S, and

$R_G^9$  is a branched or unbranched, optionally substituted  
 $C_1$ - $C_6$ -alkyl or  $C_1$ - $C_4$ -alkoxy radical or an optionally  
substituted aryl, hetaryl, arylalkyl or hetarylalkyl  
radical.

8. A pharmaceutical preparation for oral or parenteral use, comprising at least one compound as claimed in claim 1 [any of claims 1 to 5] in addition to conventional pharmaceutical excipients.

Cancel claims 9, 10 and 11.

12. A process [The use as claimed in claim 9 of the compounds as claimed in any of claims 1 to 5 for producing drugs] for the treatment of diseases in which the interaction between integrins and their natural ligands is excessive, said process comprising administering an effective amount of a drug produced from the compound of claim 1 to a mammal.
13. The process [use] as claimed in claim 12 [of the compounds as claimed in any of claims 1 to 5 for the treatment of diseases] wherein the disease is one in which the interaction between  $\alpha_v\beta_3$  integrin and its natural ligands is excessive.
14. The process [use] as claimed in claim 13 [of the compounds as claimed in any of claims 1 to 5 for the treatment of] wherein the disease is atherosclerosis, restenosis after vessel injury, angioplasty, acute kidney failure, angiogenesis-associated microangiopathies, arterial thrombosis, stroke, angiogenesis, tumor growth and metastasis, cancer, osteoporosis, high blood pressure, psoriasis or viral, parasitic or bacterial diseases, inflammations, hyperprathyroidism, Paget's disease, malignant hypercalcemia or metastatic osteolytic lesions.

Novel antagonists of integrin receptors

The invention relates to novel compounds which bind to integrin  
5 receptors, and to the preparation and use thereof.

Integrins are cell surface glycoprotein receptors which mediate  
interactions between identical and different cells and between  
cells and extracellular matrix proteins. They are involved in  
10 physiological processes such as, for example, embryogenesis,  
hemostasis, wound healing, immune response and  
formation/maintenance of tissue architecture.

Disturbances in the expression of genes of cell adhesion  
15 molecules, and disturbances of the function of receptors may  
contribute to the pathogenesis of many disorders such as, for  
example, tumors, thromboembolic events, cardiovascular disorders,  
pulmonary disorders, disorders of the CNS, of the kidney, of the  
gastrointestinal tract or inflammations.

20 Integrins are heterodimers each composed of  $\alpha$  and  $\beta$  transmembrane  
subunits, which are linked noncovalently. To date, 16 different  $\alpha$   
subunits and 8 different  $\beta$  subunits and 24 different combinations  
have been identified.

25 Integrin  $\alpha_v\beta_3$ , also called vitronectin receptor, mediates the  
adhesion to a large number of ligands - plasma proteins,  
extracellular matrix proteins, cell surface proteins - most of  
which contain the amino acid sequence RGD (Cell, 1986, 44,  
30 517-518; Science 1987, 238, 491-497), such as, for example,  
vitronectin, fibrinogen, fibronectin, von Willebrand factor,  
thrombospondin, osteopontin, laminin, collagen, thrombin,  
tenascin, MMP-2, bone sialoprotein II, various viral, parasitic  
and bacterial proteins, natural integrin antagonists such as  
35 disintegrins, neurotoxins - mambin - and leech proteins -  
decorsin, ornatin - and some non-RGD ligands such as, for  
example, Cyr-61, PECAM (L. Piali, J. Cell Biol. 1995, 130,  
451-460; Buckley, J. Cell Science 1996, 109, 437-445, J. Biol.  
Chem. 1998, 273, 3090-3096).

40 Several integrin receptors show cross-reactivity with ligands  
which contain the RGD motif. Thus, integrin  $\alpha_{IIb}\beta_3$ , also called  
platelet fibrinogen receptor, recognizes fibronectin,  
vitronectin, thrombospondin, von Willebrand factor and  
45 fibrinogen.



Integrin  $\alpha_v\beta_3$  is expressed inter alia on endothelial cells, blood platelets, monocytes/macrophages, smooth muscle cells, some B cells, fibroblasts, osteoclasts and various tumor cells such as, for example, melanomas, glioblastomas, carcinomas of the lung, breast, prostate and bladder, osteosarcomas or neuroblastomas.

Increased expression is observed under various pathological conditions such as, for example, in the prothrombotic state, when there is vessel injury, tumor growth or metastasis or reperfusion and on activated cells, in particular on endothelial cells, smooth muscle cells or macrophages.

Involvement of integrin  $\alpha_v\beta_3$  has been demonstrated inter alia for the following pathologies:

- 15 cardiovascular disorders such as atherosclerosis, restenosis after vessel injury, and angioplasty (neointima formation, smooth muscle cell migration and proliferation) (J. Vasc. Surg. 1994, 19, 125-134; Circulation 1994, 90, 2203-2206),
- 20 acute kidney failure (Kidney Int. 1994, 46, 1050-1058; Proc. Natl. Acad. Sci. 1993, 90, 5700-5704; Kidney Int. 1995, 48, 1375-1385),
- 25 angiogenesis-associated microangiopathies such as, for example, diabetic retinopathy or rheumatoid arthritis (Ann. Rev. Physiol 1987, 49, 453-464; Int. Ophthalmol. 1987, 11, 41-50; Cell 1994, 79, 1157-1164; J. Biol. Chem. 1992, 267, 10931-10934),
- 30 arterial thrombosis,  
  
stroke (phase II studies with ReoPro, Centocor Inc., 8th annual European Stroke Meeting),
- 35 cancers such as, for example, in tumor metastasis or in tumor growth (tumor-induced angiogenesis) (Cell 1991, 64, 327-336; Nature 1989, 339, 58-61; Science 1995, 270, 1500-1502),  
  
osteoporosis (bone resorption after proliferation, chemotaxis and  
40 adhesion of osteoclasts to bone matrix) (FASEB J. 1993, 7, 1475-1482; Exp. Cell Res. 1991, 195, 368-375, Cell 1991, 64, 327-336),  
  
high blood pressure, psoriasis, hyperparathyroidism, Paget's  
45 disease, malignant hypercalcemia, metastatic osteolytic lesions, inflammation, cardiac insufficiency, CHF, and for

3

antiviral, antiparasitic or antibacterial therapy and prophylaxis (adhesion and internalization).

Because of its key role, pharmaceutical preparations which  
5 contain low molecular weight integrin  $\alpha_v\beta_3$  antagonists are of great therapeutic and diagnostic benefit inter alia for the indications mentioned.

Advantageous  $\alpha_v\beta_3$  integrin receptor antagonists bind to the  
10 integrin  $\alpha_v\beta_3$  receptor with increased affinity.

Particularly advantageous  $\alpha_v\beta_3$  integrin receptor antagonists additionally show increased selectivity for integrin  $\alpha_v\beta_3$  and are less effective in relation to integrin  $\alpha_{IIb}\beta_3$  by a factor of at  
15 least 10, preferably by a factor of at least 100.

A large number of compounds such as anti- $\alpha_v\beta_3$  monoclonal antibodies, peptides containing the RGD binding sequence, natural RGD-containing proteins (for example disintegrins) and low  
20 molecular weight compounds have been shown to have an integrin  $\alpha_v\beta_3$  antagonistic effect and have demonstrated a beneficial in vivo effect (FEBS Letts 1991, 291, 50-54; J. Biol. Chem. 1990, 265, 12267-12271; J. Biol. Chem. 1994, 269, 20233-20238; J. Cell Biol 1993, 51, 206-218; J. Biol. Chem. 1987, 262, 17703-17711;  
25 Bioorg. Med. Chem. 1998, 6, 1185-1208).

Also known are  $\alpha_v\beta_3$  antagonists with a tricyclic molecular structure.

30 WO 9915508-A1, WO 9830542-A1 and WO 9701540-A1 describe dibenzocycloheptane derivatives, WO 9911626-A1 describes dibenzo[1,4]oxazepine derivatives and WO 9905107-A1 describes benzocycloheptane derivatives.

35 It is an object of the present invention to provide novel integrin receptor antagonists with advantageous properties.

We have found that this object is achieved by compounds of the formula I

40

B-G-L

I

where B, G and L have the following meanings:

45

L a structural element of the formula  $I_L$

-U-T

$I_L$

5 where

T is a COOH group or a radical which can be hydrolyzed to COOH and

10 -U- is  $-(X_L)_a-(CR_L^1R_L^2)_b-$ ,  $-CR_L^1=CR_L^2-$ , ethynylene or  $=CR_L^1-$ , where

a is 0 or 1,

15 b is 0, 1 or 2

$X_L$  is  $CR_L^3R_L^4$ ,  $NR_L^5$ , oxygen or sulfur,

$R_L^1$ ,  $R_L^2$ ,  $R_L^3$ ,  $R_L^4$

20 are, independently of one another, hydrogen, -T, -OH,  $-NR_L^6R_L^7$ ,  $-CO-NH_2$ , a halogen radical, a branched or unbranched, optionally substituted  $C_1$ - $C_6$ -alkyl,  $C_2$ - $C_6$ -alkenyl,  $C_2$ - $C_6$ -alkynyl,  $C_3$ - $C_7$ -cycloalkyl,  $-CO-NH(C_1$ - $C_6$ -alkyl),  $-CO-N(C_1$ - $C_6$ -alkyl) $_2$  or  
25  $C_1$ - $C_4$ -alkoxy radical, an optionally substituted  $C_1$ - $C_2$ -alkylene-T,  $C_2$ -alkenylene-T or  $C_2$ -alkynylene-T radical, an optionally substituted aryl or arylalkyl radical or, in each case independently of one another, two radicals  $R_L^1$  and  $R_L^2$  or  $R_L^3$  and  $R_L^4$  or,  
30 where appropriate,  $R_L^1$  and  $R_L^3$  together are an optionally substituted 3- to 7-membered saturated or unsaturated carbocyclic or heterocyclic system which may contain up to three different or identical heteroatoms O, N, S,

35

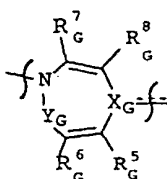
$R_L^5$ ,  $R_L^6$ ,  $R_L^7$

are, independently of one another, hydrogen, a branched or unbranched, optionally substituted  $C_1$ - $C_6$ -alkyl,  $C_3$ - $C_7$ -cycloalkyl,  $CO-O-C_1$ - $C_6$ -alkyl,  $SO_2-C_1$ - $C_6$ -alkyl or  $CO-C_1$ - $C_6$ -alkyl radical or an  
40 optionally substituted  $CO-O$ -alkylene-aryl,  $SO_2$ -aryl,  $CO$ -aryl,  $SO_2$ -alkylene-aryl or  $CO$ -alkylene-aryl radical,

45

G a structural element of the formula  $I_G$

5



I<sub>G</sub>

5

where

10 the structural element G can be incorporated in both orientations, and

X<sub>G</sub> is nitrogen or CR<sub>G</sub><sup>1</sup> in the case where structural element G is connected to structural element L or B via X<sub>G</sub> by a single bond,

15

or

is carbon in the case where structural element G is connected to structural element L via X<sub>G</sub> by a double bond,

20

Y<sub>G</sub> is CO, CS, C=NR<sub>G</sub><sup>2</sup> or CR<sub>G</sub><sup>3</sup>R<sub>G</sub><sup>4</sup>,

25

where

R<sub>G</sub><sup>1</sup> is hydrogen, halogen, a hydroxyl group or a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl or C<sub>1</sub>-C<sub>4</sub>-alkoxy radical,

30

R<sub>G</sub><sup>2</sup> is hydrogen, a hydroxyl group, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl or -O-C<sub>3</sub>-C<sub>7</sub>-cycloalkyl radical or an optionally substituted aryl, -O-aryl, arylalkyl or -O-alkylene-aryl radical and

35

R<sub>G</sub><sup>3</sup>, R<sub>G</sub><sup>4</sup> are, independently of one another, hydrogen or a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkynyl or C<sub>1</sub>-C<sub>4</sub>-alkoxy radical or the two R<sub>G</sub><sup>3</sup> and R<sub>G</sub><sup>4</sup> radicals together are a cyclic acetal -O-CH<sub>2</sub>-CH<sub>2</sub>-O- or -O-CH<sub>2</sub>-O- or the two R<sub>G</sub><sup>3</sup> and R<sub>G</sub><sup>4</sup> radicals together are an optionally substituted C<sub>3</sub>-C<sub>7</sub>-cycloalkyl radical,

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45

$R_G^5, R_G^6, R_G^7, R_G^8$

are, independently of one another, hydrogen, an amino or hydroxyl group, an  $HN-CO-R_G^9$  radical, a branched or unbranched, optionally substituted  $C_1-C_6$ -alkyl or  $C_1-C_4$ -alkoxy radical, an optionally substituted aryl or arylalkyl radical or, independently of one another, in each case two  $R_G^5$  and  $R_G^6$  or  $R_G^7$  and  $R_G^8$  radicals together are an optionally substituted, fused-on, unsaturated or aromatic 3- to 6-membered carbocyclic or heterocyclic system which may contain up to three different or identical heteroatoms O, N, S, and

$R_G^9$  is a branched or unbranched, optionally substituted  $C_1-C_6$ -alkyl or  $C_1-C_4$ -alkoxy radical or an optionally substituted aryl, hetaryl, arylalkyl or hetarylalkyl radical,

B a structural element containing at least one atom which, under physiological conditions, can as hydrogen acceptor form hydrogen bonds, where the distance between at least one hydrogen acceptor atom and the structural element G along the shortest possible route along the structural element framework is from 4 to 13 atomic bonds,

and the physiologically tolerated salts, prodrugs and the enantiomerically pure or diastereomerically pure and tautomeric forms.

T in structural element L means a COOH group or a radical which can be hydrolyzed to COOH. A radical which can be hydrolyzed to COOH means a radical which is converted into a COOH group after hydrolysis.

An example which may be mentioned of a radical T which can be hydrolyzed to COOH is the group



in which  $R^1$  has the following meaning:

a) OM where M can be a metal cation such as an alkali metal cation such as lithium, sodium, potassium, the equivalent of an alkaline earth metal cation such as calcium, magnesium and barium or an environmentally compatible organic ammonium ion such as, for example, primary, secondary, tertiary or

quaternary C<sub>1</sub>-C<sub>4</sub>-alkylammonium or ammonium ion, such as, for example, ONa, OK or OLi,

- b) a branched or unbranched, optionally halogen-substituted  
 5 C<sub>1</sub>-C<sub>8</sub>-alkoxy radical such as, for example, methoxy, ethoxy, propoxy, 1-methylethoxy, butoxy, 1-methylpropoxy, 2-methylpropoxy, 1,1-dimethylethoxy, in particular methoxy, ethoxy, 1-methylethoxy, pentoxy, hexoxy, heptoxy, octoxy, difluoromethoxy, trifluoromethoxy, chlorodifluoromethoxy,  
 10 1-fluoroethoxy, 2-fluoroethoxy, 2,2-difluoroethoxy, 1,1,2,2-tetrafluoroethoxy, 2,2,2-trifluoroethoxy, 2-chloro-1,1,2-trifluoroethoxy or pentafluoroethoxy
- c) a branched or unbranched, optionally halogen-substituted  
 15 C<sub>1</sub>-C<sub>4</sub>-alkylthio radical such as methylthio, ethylthio, propylthio, 1-methylethylthio, butylthio, 1-methylpropylthio, 2-methylpropylthio or 1,1-dimethylethylthio radical
- d) an optionally substituted -O-alkylene-aryl radical such as,  
 20 for example, -O-benzyl
- e) R<sup>1</sup> also a radical -(O)<sub>m</sub>-N(R<sup>18</sup>)(R<sup>19</sup>),  
 in which m is 0 or 1, and R<sup>18</sup> and R<sup>19</sup>, which may be identical  
 or different, have the following meaning:  
 25 hydrogen,
- a branched or unbranched, optionally substituted
- 30 C<sub>1</sub>-C<sub>6</sub>-alkyl radical such as, for example, methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1-methylpentyl, 1,2-dimethylbutyl,  
 35 1,3-dimethylbutyl, 2,3-dimethylbutyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethylbutyl, 2-ethylbutyl or 1-ethyl-2-methylpropyl or the corresponding substituted radicals, preferably methyl, ethyl, propyl, butyl or i-butyl,  
 40
- 45 C<sub>2</sub>-C<sub>6</sub>-alkenyl radical such as, for example, vinyl, 2-propenyl, 2-butenyl, 3-butenyl, 1-methyl-2-propenyl, 2-methyl-2-propenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-methyl-2-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 1-methyl-3-butenyl, 2-methyl-3-butenyl, 3-methyl-3-butenyl, 1,1-dimethyl-2-propenyl, 1,2-dimethyl-2-propenyl, 1-ethyl-2-propenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl,

45

or  $R^{18}$  and  $R^{19}$  together form a  $C_4$ - $C_7$ -alkylene chain which is closed to a ring, is optionally substituted, for example by  $C_1$ - $C_4$ -alkyl, and may contain a heteroatom selected from the group of oxygen, sulfur or nitrogen, such as, for example,

- 5  $-(CH_2)_4-$ ,  $-(CH_2)_5-$ ,  $-(CH_2)_6-$ ,  $-(CH_2)_7-$ ,  $-(CH_2)_2-O-(CH_2)_2-$ ,  
 $-CH_2-S-(CH_2)_3-$ ,  $-(CH_2)_2-O-(CH_2)_3-$ ,  $-NH-(CH_2)_3-$ ,  $-CH_2-NH-(CH_2)_2-$ ,  
 $-CH_2-CH=CH-CH_2-$ ,  $-CH=CH-(CH_2)_3-$ ,  $-CO-(CH_2)_2-CO-$  or  
 $-CO-(CH_2)_3-CO-$ .

- 10 Preferred T radicals are  $-COOH$ ,  $-CO-O-C_1-C_8$ -alkyl or  $-CO-O$ -benzyl.

The radical  $-U-$  in the structural element L is a spacer selected from the group of  $-(X_L)_a-(CR_L^1R_L^2)_b-$ ,  $-CR_L^1=CR_L^2-$ , ethynylene or  $=CR_L^1-$ . In the case of the  $=CR_L^1-$  radical, the structural element

- 15 L is linked by a double bond to the structural element G.

$X_L$  is preferably the radical  $CR_L^3R_L^4$ ,  $NR_L^5$ , oxygen or sulfur.

Preferred  $-U-$  radicals are the radicals  $=CR_L^1-$  or

- 20  $-(X_L)_a-(CR_L^1R_L^2)_b-$ , where  $X_L$  is preferably  $CR_L^3R_L^4$  ( $a = 0$  or  $1$ ) or oxygen ( $a = 1$ ).

Particularly preferred  $-U-$  radicals are the radicals

- 25  $-(X_L)_a-(CR_L^1R_L^2)_b-$ , where  $X_L$  is preferably  $CR_L^3R_L^4$  ( $a = 1$ ) or oxygen ( $a = 1$ ).

A halogen radical for  $R_L^1$ ,  $R_L^2$ ,  $R_L^3$  or  $R_L^4$  in structural element L means, for example, F, Cl, Br or I, preferably F.

- 30 A branched or unbranched  $C_1$ - $C_6$ -alkyl radical for  $R_L^1$ ,  $R_L^2$ ,  $R_L^3$  or  $R_L^4$  in structural element L means, for example, methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl,  
 35 1-ethylpropyl, hexyl, 1-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethylbutyl, 2-ethylbutyl or 1-ethyl-2-methylpropyl, preferably branched or unbranched  $C_1$ - $C_4$ -alkyl  
 40 radicals such as, for example, methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl, particularly preferably methyl.

A branched or unbranched  $C_2$ - $C_6$ -alkenyl radical for  $R_L^1$ ,  $R_L^2$ ,  $R_L^3$  or

- 45  $R_L^4$  in structural element L means, for example, vinyl, 2-propenyl, 2-butenyl, 3-butenyl, 1-methyl-2-propenyl, 2-methyl-2-propenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-methyl-2-butenyl,



- 2-methyl-2-butenyl, 3-methyl-2-butenyl, 1-methyl-3-butenyl,  
 2-methyl-3-butenyl, 3-methyl-3-butenyl, 1,1-dimethyl-2-propenyl,  
 1,2-dimethyl-2-propenyl, 1-ethyl-2-propenyl, 2-hexenyl,  
 3-hexenyl, 4-hexenyl, 5-hexenyl, 1-methyl-2-pentenyl,  
 5 2-methyl-2-pentenyl, 3-methyl-2-pentenyl, 4-methyl-2-pentenyl,  
 3-methyl-3-pentenyl, 4-methyl-3-pentenyl, 1-methyl-4-pentenyl,  
 2-methyl-4-pentenyl, 3-methyl-4-pentenyl, 4-methyl-4-pentenyl,  
 1,1-dimethyl-2-butenyl, 1,1-dimethyl-3-butenyl,  
 1,2-dimethyl-2-butenyl, 1,2-dimethyl-3-butenyl,  
 10 1,3-dimethyl-2-butenyl, 1,3-dimethyl-3-butenyl, 2,2-dimethyl-  
 3-butenyl, 2,3-dimethyl-2-butenyl, 2,3-dimethyl-3-butenyl,  
 1-ethyl-2-butenyl, 1-ethyl-3-butenyl, 2-ethyl-2-butenyl,  
 2-ethyl-3-butenyl, 1,1,2-trimethyl-2-propenyl, 1-ethyl-1-  
 methyl-2-propenyl and 1-ethyl-2-methyl-2-propenyl, in particular  
 15 2-propenyl, 2-butenyl, 3-methyl-2-butenyl or 3-methyl-2-pentenyl.

- A branched or unbranched  $C_2$ - $C_6$ -alkynyl radical for  $R_L^1$ ,  $R_L^2$ ,  $R_L^3$  or  
 $R_L^4$  in structural element L means, for example, ethynyl,  
 2-propynyl, 2-butyne, 3-butyne, 1-methyl-2-propynyl,  
 20 2-pentyne, 3-pentyne, 4-pentyne, 1-methyl-3-butyne,  
 2-methyl-3-butyne, 1-methyl-2-butyne, 1,1-dimethyl-2-propynyl,  
 1-ethyl-2-propynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl,  
 1-methyl-2-pentyne, 1-methyl-2-pentyne, 1-methyl-3-pentyne,  
 1-methyl-4-pentyne, 2-methyl-3-pentyne, 2-methyl-4-pentyne,  
 25 3-methyl-4-pentyne, 4-methyl-2-pentyne, 1,1-dimethyl-2-  
 butyne, 1,1-dimethyl-3-butyne, 1,2-dimethyl-3-butyne,  
 2,2-dimethyl-3-butyne, 1-ethyl-2-butyne, 1-ethyl-3-butyne,  
 2-ethyl-3-butyne and 1-ethyl-1-methyl-2-propynyl, preferably  
 ethynyl, 2-propynyl, 2-butyne, 1-methyl-2-propynyl or  
 30 1-methyl-2-butyne.

A branched or unbranched  $C_3$ - $C_7$ -cycloalkyl radical for  $R_L^1$ ,  $R_L^2$ ,  $R_L^3$   
 or  $R_L^4$  in structural element L means, for example, cyclopropyl,  
 cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

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A branched or unbranched  $C_1$ - $C_4$ -alkoxy radical for  $R_L^1$ ,  $R_L^2$ ,  $R_L^3$  or  
 $R_L^4$  in structural element L means, for example, methoxy, ethoxy,  
 propoxy, 1-methylethoxy, butoxy, 1-methylpropoxy, 2-methylpropoxy  
 or 1,1-dimethylethoxy.

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The radicals  $-CO-NH(C_1-C_6-alkyl)$  and  $-CO-N(C_1-C_6-alkyl)_2$  are  
 respectively secondary and tertiary amides and are composed of  
 the amide linkage and the appropriate  $C_1$ - $C_6$ -alkyl radicals as  
 described above for  $R_L^1$ ,  $R_L^2$ ,  $R_L^3$  or  $R_L^4$ .

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The  $R_L^1$ ,  $R_L^2$ ,  $R_L^3$  or  $R_L^4$  radicals may further be a radical

C<sub>1</sub>-C<sub>2</sub>-alkylene-T such as, for example, methylene-T or ethylene-T,  
C<sub>2</sub>-alkenylene-T such as, for example, ethenylene-T or  
C<sub>2</sub>-alkynylene-T such as, for example, ethynylene-T,

- 5 an aryl radical such as, for example, phenyl, 1-naphthyl or  
2-naphthyl or

an arylalkyl radical such as, for example, benzyl or phenethyl

- 10 it being possible for the radicals to be substituted where appropriate.

It is also possible for, in each case independently of one another, two radicals  $R_L^1$  and  $R_L^2$  or  $R_L^3$  and  $R_L^4$  or, where

- 15 appropriate,  $R_L^1$  and  $R_L^3$  together to be an optionally substituted  
3- to 7-membered saturated or unsaturated carbocyclic or  
heterocyclic system which may contain up to three different or  
identical heteroatoms O, N, S.

- 20 All radicals for  $R_L^1$ ,  $R_L^2$ ,  $R_L^3$  or  $R_L^4$  may optionally be substituted. Unless the substituents are specified, independently of one another up to 5 substituents are suitable for the radicals  $R_L^1$ ,  $R_L^2$ ,  $R_L^3$  or  $R_L^4$  and all other substituted radicals in the description hereinafter, for example selected from the following
- 25 group:

-NO<sub>2</sub>, -NH<sub>2</sub>, -OH, -CN, -COOH, -O-CH<sub>2</sub>-COOH, halogen, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>4</sub>-alkyl such as, for example, methyl, CF<sub>3</sub>, C<sub>2</sub>F<sub>5</sub> or CH<sub>2</sub>F, -CO-O-C<sub>1</sub>-C<sub>4</sub>-alkyl,

- 30 C<sub>3</sub>-C<sub>6</sub>-cycloalkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>4</sub>-alkylthio,  
-NH-CO-O-C<sub>1</sub>-C<sub>4</sub>-alkyl, -O-CH<sub>2</sub>-COO-C<sub>1</sub>-C<sub>4</sub>-alkyl, -NH-CO-C<sub>1</sub>-C<sub>4</sub>-alkyl,  
-CO-NH-C<sub>1</sub>-C<sub>4</sub>-alkyl, -NH-SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub>-alkyl, -SO<sub>2</sub>-NH-C<sub>1</sub>-C<sub>4</sub>-alkyl,  
-N(C<sub>1</sub>-C<sub>4</sub>-alkyl)<sub>2</sub>, -NH-C<sub>1</sub>-C<sub>4</sub>-alkyl or -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub>-alkyl radical, such  
as, for example, -SO<sub>2</sub>-CF<sub>3</sub>, an optionally substituted -NH-CO-aryl,  
35 -CO-NH-aryl, -NH-CO-O-aryl, -NH-CO-O-alkylene-aryl, -NH-SO<sub>2</sub>-aryl,  
-SO<sub>2</sub>-NH-aryl, -CO-NH-benzyl, -NH-SO<sub>2</sub>-benzyl or -SO<sub>2</sub>-NH-benzyl  
radical, an optionally substituted -SO<sub>2</sub>-NR<sup>2</sup>R<sup>3</sup> or -CO-NR<sup>2</sup>R<sup>3</sup>  
radical, where the radicals R<sup>2</sup> and R<sup>3</sup> may, independently of one  
another, have the meaning of R<sub>L</sub><sup>5</sup> hereinafter, or the two radicals  
40 R<sup>2</sup> and R<sup>3</sup> together are a 3- to 6-membered, optionally substituted,  
saturated, unsaturated or aromatic heterocyclic system which, in  
addition to the ring nitrogen, may contain up to three other  
different or identical heteroatoms O, N, S, and optionally two  
radicals substituting this heterocyclic system together are a  
45 fused-on or saturated, unsaturated or aromatic carbocyclic or  
heterocyclic system which may contain up to three different or  
identical heteroatoms O, N, S, and the ring can optionally be

substituted or another, optionally substituted ring can be fused onto this ring.

Unless specified, two substituents on all terminally bonded,  
5 substituted hetaryl radicals in the description may form a  
fused-on, 5- to 7-membered, unsaturated or aromatic carbocyclic  
system.

Preferred  $R_L^1$ ,  $R_L^2$ ,  $R_L^3$  or  $R_L^4$  radicals are, independently of one  
10 another, hydrogen, halogen, a branched or unbranched, optionally  
substituted  $C_1$ - $C_4$ -alkyl,  $C_1$ - $C_4$ -alkoxy or  $C_3$ - $C_7$ -cycloalkyl radical  
or the  $-NR_L^6R_L^7$  radical.

Particularly preferred  $R_L^1$ ,  $R_L^2$ ,  $R_L^3$  or  $R_L^4$  radicals are,  
15 independently of one another, hydrogen, fluorine or a branched or  
unbranched, optionally substituted  $C_1$ - $C_4$ -alkyl radical, preferably  
methyl.

The  $R_L^5$ ,  $R_L^6$ ,  $R_L^7$  radicals in the structural element L are,  
20 independently of one another, hydrogen, a branched or unbranched,  
optionally substituted

C<sub>1</sub>-C<sub>6</sub>-alkyl radical, for example as described above for R<sub>L</sub><sup>1</sup>,

25 C<sub>3</sub>-C<sub>7</sub>-cycloalkyl radical, for example as described above for R<sub>L</sub><sup>1</sup>,

CO-O-C<sub>1</sub>-C<sub>6</sub>-alkyl, SO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub>-alkyl or CO-C<sub>1</sub>-C<sub>6</sub>-alkyl radical which is composed of the group CO-O, SO<sub>2</sub> or CO and, for example, of the C<sub>1</sub>-C<sub>6</sub>-alkyl radicals described above for R<sub>1</sub><sup>1</sup>,

30 or an optionally substituted CO-O-alkylene-aryl,  
SO<sub>2</sub>-aryl, SO<sub>2</sub>-alkylene-aryl or CO-alkylene-aryl radical which is  
composed of the group CO-O, SO<sub>2</sub>, or CO and, for example, of the  
aryl or arylalkyl radicals described above for R<sub>1</sub><sup>1</sup>.

35 Preferred  $R_L^6$  radicals in the structural element L are hydrogen, a  
branched or unbranched, optionally substituted  $C_1$ - $C_4$ -alkyl,  
CO-O- $C_1$ - $C_4$ -alkyl, CO- $C_1$ - $C_4$ -alkyl or  $SO_2$ - $C_1$ - $C_4$ -alkyl radical or an  
optionally substituted CO-O-benzyl,  $SO_2$ -aryl,  $SO_2$ -alkylene-aryl or  
40 CO-aryl radical.

Preferred  $R_L^7$  radicals in the structural element L are hydrogen or a branched or unbranched, optionally substituted  $C_1$ - $C_4$ -alkyl radical.

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R<sub>G</sub><sup>2</sup> in structural element G is hydrogen, a hydroxyl group, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy or C<sub>3</sub>-C<sub>7</sub>-cycloalkyl radical, for example as described  
45 above in each case for R<sub>L</sub><sup>1</sup>,

an optionally substituted -O-C<sub>3</sub>-C<sub>7</sub>-cycloalkyl radical which is composed of an ether group and, for example, of the C<sub>3</sub>-C<sub>7</sub>-cycloalkyl radical described above for R<sub>L</sub><sup>1</sup>,

- 5 an optionally substituted aryl or arylalkyl radical, for example as described above in each case for  $R_L^1$ , or

an optionally substituted -O-aryl or -O-alkylene-aryl radical which is composed of a -O- group and, for example, of the aryl or

- 10 arylalkyl radicals described above for  $R_L^1$ .

Branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkynyl or C<sub>1</sub>-C<sub>4</sub>-alkoxy radicals for R<sub>G</sub><sup>3</sup> or R<sub>G</sub><sup>4</sup> in structural element G mean, independently of one another,

- 15 for example the corresponding radicals described above in each case for  $R_r^1$ .

It is also possible for the two radicals  $R_G^3$  and  $R_G^4$  together to form a cyclic acetal such as, for example,  $-O-CH_2-CH_2-O-$  or

- 20  $-O-CH_2-O-$ .

A further possibility is for the two radicals  $R_G^3$  and  $R_G^4$  together to form an optionally substituted  $C_3$ - $C_7$ -cycloalkyl radical.

- 25 Preferred  $R_G^3$  or  $R_G^4$  radicals are, independently of one another, hydrogen,  $C_1$ - $C_4$ -alkyl or  $C_1$ - $C_4$ -alkoxy.

Branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl or C<sub>1</sub>-C<sub>4</sub>-alkoxy radicals and optionally substituted aryl or arylalkyl radicals for R<sub>G</sub><sup>5</sup>, R<sub>G</sub><sup>6</sup>, R<sub>G</sub><sup>7</sup> or R<sub>G</sub><sup>8</sup> in structural element G mean, independently of one another, for example the corresponding radicals described above in each case for R<sub>R</sub><sup>1</sup>.

- 30 radicals for  $R_G^5$ ,  $R_G^6$ ,  $R_G^7$  or  $R_G^8$  in structural element G mean, independently of one another, for example the corresponding radicals described above in each case for  $R_L^1$ .

It is also possible for in each case two radicals  $R_G^5$  and  $R_G^6$  or  $R_G^7$  and  $R_G^8$  independently of one another together to form an

- 35 optionally substituted, fused-on, unsaturated or aromatic 3- to 6-membered carbocyclic or heterocyclic system which may contain up to three different or identical heteroatoms O, N, S.

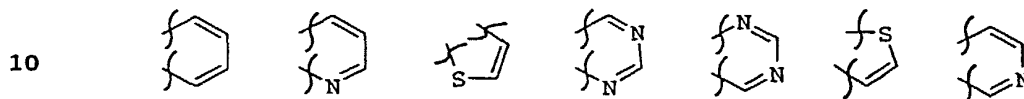
Preferred  $R_G^5$ ,  $R_G^6$ ,  $R_G^7$  or  $R_G^8$  radicals are, independently of one

- 40 another, hydrogen or optionally substituted aryl radicals, preferably phenyl or arylalkyl radicals, preferably benzyl, and in each case two radicals  $R_G^5$  and  $R_G^6$  or  $R_G^7$  and  $R_G^8$  together are an optionally substituted, fused-on, unsaturated or aromatic 3- to 6-membered carbocyclic or heterocyclic system which may  
45 contain up to three different or identical heteroatoms O, N, S.

## 15

With particularly preferred radicals for  $R_G^5$ ,  $R_G^6$ ,  $R_G^7$  or  $R_G^8$ , independently of one another in each case two radicals  $R_G^5$  and  $R_G^6$  or  $R_G^7$  and  $R_G^8$  together form an optionally substituted, fused-on, unsaturated or aromatic 3- to 6-membered carbocyclic or

5 heterocyclic system selected from one of the following doubly linked structural formulae:



A branched or unbranched, optionally substituted  $C_1$ - $C_6$ -alkyl or

15  $C_1$ - $C_4$ -alkoxy radical and an optionally substituted aryl or arylalkyl radical for  $R_G^9$  mean, for example, the corresponding radicals described above for  $R_L^1$ .

A hetaryl radical for  $R_G^9$  means, for example, radicals such as

20 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-furyl, 3-furyl, 2-pyrrolyl, 3-pyrrolyl, 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-pyrimidyl, 4-pyrimidyl, 5-pyrimidyl, 6-pyrimidyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl,

25 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, thiadiazolyl, oxadiazolyl or triazinyl.

30 Substituted hetaryl radicals for  $R_G^9$  mean, as described above generally for terminal, substituted hetaryl radicals, also fused-on derivatives of the abovementioned hetaryl radicals, such as, for example, indazole, indole, benzothiophene, benzofuran, indoline, benzimidazole, benzothiazole, benzoxazole, quinoline or

35 isoquinoline radicals.

A hetarylalkyl radical for  $R_G^9$  means radicals composed, for example, of the  $C_1$ - $C_6$ -alkyl radicals described above and of the hetaryl radicals described above, such as, preferably, the

40 radicals  $-CH_2$ -2-pyridyl,  $-CH_2$ -3-pyridyl,  $-CH_2$ -4-pyridyl,  $-CH_2$ -2-thienyl,  $-CH_2$ -3-thienyl,  $-CH_2$ -2-thiazolyl,  $-CH_2$ -4-thiazolyl,  $-CH_2$ -5-thiazolyl,  $-CH_2$ - $CH_2$ -2-pyridyl,  $-CH_2$ - $CH_2$ -3-pyridyl,  $-CH_2$ - $CH_2$ -4-pyridyl,  $-CH_2$ - $CH_2$ -2-thienyl,  $-CH_2$ - $CH_2$ -3-thienyl,  $-CH_2$ - $CH_2$ -2-thiazolyl,  $-CH_2$ - $CH_2$ -4-thiazolyl or

45  $-CH_2$ - $CH_2$ -5-thiazolyl.

Preferred structural elements G are composed of the preferred radicals of the structural element.

Particularly preferred structural elements G are composed of the particularly preferred radicals of the structural element.

Structural element B means a structural element containing at least one atom which, under physiological conditions, can as hydrogen acceptor form hydrogen bonds, where the distance between at least one hydrogen acceptor atom and the structural element G along the shortest possible route along the structural element framework is from 4 to 13 atomic bonds. The design of the structural framework of the structural element B can be varied widely.

Examples of suitable atoms which, under physiological conditions, can as hydrogen acceptors form hydrogen bonds are atoms with Lewis base properties such as, for example, the heteroatoms nitrogen, oxygen or sulfur.

Physiological conditions mean a pH prevailing at the site in an organism where the ligands interact with the receptors. In the present case, the physiological conditions have a pH of, for example, 5 to 9.

In a preferred embodiment, the structural element B is a structural element of the formula  $I_B$



where A and E have the following meanings:

A a structural element selected from the group:

a 5- to 7-membered monocyclic saturated, unsaturated or aromatic ring having 0 to 4 heteroatoms selected from the group of O, N or S, it being possible, in each case independently of one another, for the ring nitrogen which is present where appropriate or all carbons to be substituted, with the proviso that at least one heteroatom selected from the group of O, N or S is present in the structural element A,

or

17  
a 9- to 14-membered polycyclic saturated, unsaturated or aromatic system having up to 6 heteroatoms selected from the group of N, O or S, it being possible, in each case independently of one another, for the ring nitrogen which is present where appropriate or all carbons to be substituted, with the proviso that at least one heteroatom selected from the group of O, N or S is present in the structural element A,

5 or

a radical

15



where

20  $Z_A^1$  is oxygen, sulfur or optionally substituted nitrogen and

$Z_A^2$  is optionally substituted nitrogen, oxygen or sulfur,

25

and

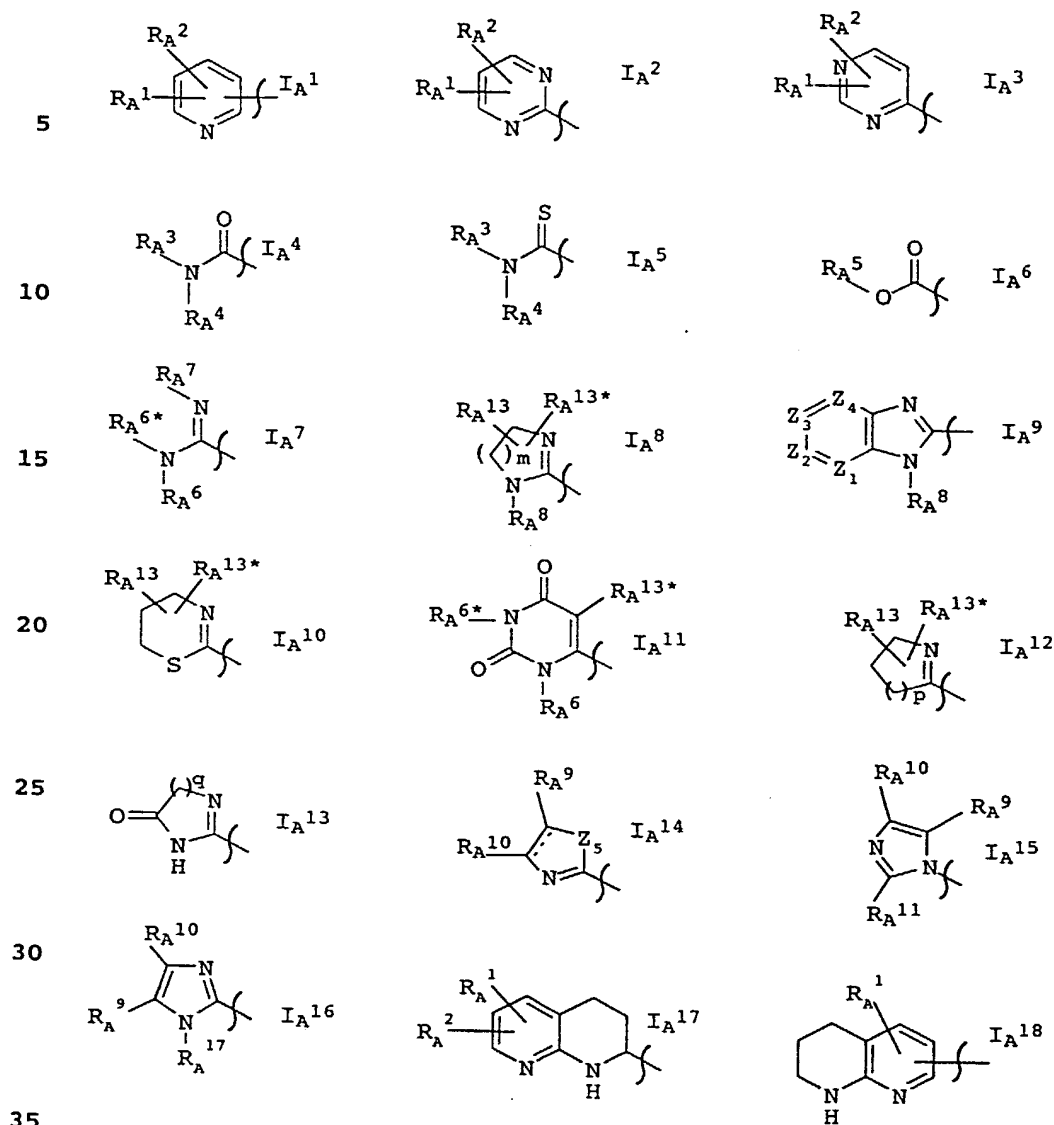
E a spacer structural element which connects structural element A to structural element G covalently, where the number of atomic bonds along the shortest possible route along the structural element framework E is from 4 to 12.

In a particularly preferred embodiment, the structural element A is a structural element selected from the group of structural elements of the formulae  $I_A^1$  to  $I_A^{18}$ ,

40

45







$X_A$  can be  $-SO_2-$ ,  $-S-$ ,  $-O-$ ,  $-CO-$ ,  $-O-CO-$ ,  $-CO-O-$ ,  
 $-CO-N(R_A^{12})-$ ,  $-N(R_A^{12})-CO-$ ,  $-N(R_A^{12})-SO_2-$  or  
 $-SO_2-N(R_A^{12})-$  and

- 5  $R_A^{12}$  can be hydrogen, a branched or unbranched, optionally substituted  $C_1-C_6$ -alkyl,  $C_1-C_4$ -alkoxy,  $-O$ -alkylene-aryl or  $-O$ -aryl radical, an amino radical with primary or, where appropriate, secondary or tertiary substitution, an optionally  $C_1-C_4$ -alkyl- or
- 10 aryl-substituted  $C_2-C_6$ -alkynyl or  $C_2-C_6$ -alkenyl radical or a 3- to 6-membered, saturated or unsaturated heterocyclic system which is substituted by up to three identical or different radicals and which may contain up to three different or identical
- 15 heteroatoms O, N, S,  $C_3-C_7$ -cycloalkyl, aryl or hetaryl radical, it being possible for two radicals together to be a fused-on, saturated, unsaturated or aromatic carbocyclic or heterocyclic system which may contain up to three different or identical
- 20 heteroatoms O, N, S, and the ring may optionally be substituted, or another, optionally substituted, saturated, unsaturated or aromatic ring may be fused onto this ring,
- 25  $R_A^5$  is a branched or unbranched, optionally substituted  $C_1-C_6$ -alkyl, arylalkyl,  $C_3-C_7$ -cycloalkyl or  $C_1-C_6$ -alkyl- $C_3-C_7$ -cycloalkyl radical or an optionally substituted aryl radical,
- 30  $R_A^6$ ,  $R_A^{6*}$  are hydrogen, a branched or unbranched, optionally substituted  $C_1-C_4$ -alkyl,  $-CO-O-C_1-C_4$ -alkyl, arylalkyl,  $-CO-O$ -alkylene-aryl,  $-CO-O$ -allyl,  $-CO-C_1-C_4$ -alkyl,  $-CO$ -alkylene-aryl,  $C_3-C_7$ -cycloalkyl or  $-CO$ -allyl radical
- 35 or the two radicals  $R_A^6$  and  $R_A^{6*}$  in the structural element  $I_A^7$  together are an optionally substituted, saturated, unsaturated or aromatic heterocyclic system which may, in addition to the ring nitrogen, contain up to two further different or identical heteroatoms O, N, S,
- 40  $R_A^7$  is hydrogen,  $-OH$ ,  $-CN$ ,  $-CONH_2$ , a branched or unbranched, optionally substituted  $C_1-C_4$ -alkyl,  $C_1-C_4$ -alkoxy,  $C_3-C_7$ -cycloalkyl or  $-O-CO-C_1-C_4$ -alkyl radical, or an optionally substituted arylalkyl,  $-O$ -alkylene-aryl,
- 45  $-O-CO$ -aryl,  $-O-CO$ -alkylene-aryl or  $-O-CO$ -allyl radical, or the two radicals  $R_A^6$  and  $R_A^7$  together are an optionally substituted, unsaturated or aromatic heterocyclic system

which may, in addition to the ring nitrogen, contain up to two further different or identical heteroatoms O, N, S,

5         $R_A^8$  is hydrogen, a branched or unbranched, optionally  
substituted  $C_1$ - $C_4$ -alkyl, CO- $C_1$ - $C_4$ -alkyl,  $SO_2$ - $C_1$ - $C_4$ -alkyl  
or CO-O- $C_1$ - $C_4$ -alkyl radical or an optionally substituted  
aryl, CO-aryl,  $SO_2$ -aryl, CO-O-aryl, CO-alkylene-aryl,  
10         $SO_2$ -alkylene-aryl, CO-O-alkylene-aryl or alkylene-aryl  
radical,

$R_A^9$ ,  $R_A^{10}$   
are, independently of one another, hydrogen, -CN,  
halogen, a branched or unbranched, optionally substituted  
15  $C_1$ - $C_6$ -alkyl radical or an optionally substituted aryl,  
arylalkyl, hetaryl,  $C_3$ - $C_7$ -cycloalkyl radical or a  
 $CO-O-R_A^{14}$ ,  $O-R_A^{14}$ ,  $S-R_A^{14}$ ,  $NR_A^{15}R_A^{16}$  or  $CO-NR_A^{15}R_A^{16}$  radical,  
or the two  $R_A^9$  and  $R_A^{10}$  radicals in the structural element  
20  $I_A^{14}$  together are a 5- to 7-membered saturated,  
unsaturated or aromatic carbocyclic or heterocyclic  
system which may contain up to three different or  
identical heteroatoms O, N, S and is optionally  
substituted by up to three identical or different  
radicals,

$R_A^{11}$  is hydrogen, -CN, halogen, a branched or unbranched, optionally substituted  $C_1$ - $C_6$ -alkyl radical or an optionally substituted aryl, arylalkyl, hetaryl,  $C_3$ - $C_7$ -cycloalkyl radical or a  $CO-O-R_A^{14}$ ,  $O-R_A^{14}$ ,  $S-R_A^{14}$ ,  $NR_A^{15}R_A^{16}$  or  $CO-NR_A^{15}R_A^{16}$  radical,

35  $R_A^{17}$  in the structural element  $I_A^{16}$  the two radicals  $R_A^9$  and  $R_A^{17}$  together are a 5- to 7-membered saturated, unsaturated or aromatic heterocyclic system which may, in addition to the ring nitrogen, contain up to three different or identical heteroatoms O, N, S, and is optionally substituted by up to three identical or different radicals.

40       $Z^1, Z^2, Z^3, Z^4$   
are, independently of one another, nitrogen, C-H,  
C-halogen or a branched or unbranched, optionally  
substituted C-C<sub>1</sub>-C<sub>4</sub>-alkyl or C-C<sub>1</sub>-C<sub>4</sub>-alkoxy radical,

45  $Z^5$  is  $NR_A^8$ , oxygen or sulfur.

- 5 A branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl radical for R<sub>A</sub><sup>1</sup> or R<sub>A</sub><sup>2</sup> means, independently of one another, for example the corresponding radicals described above for R<sub>L</sub><sup>1</sup>, preferably methyl or trifluoromethyl.
- 10 The branched or unbranched, optionally substituted CO-C<sub>1</sub>-C<sub>6</sub>-alkyl radical for R<sub>A</sub><sup>1</sup> or R<sub>A</sub><sup>2</sup> in the structural elements I<sub>A</sub><sup>1</sup>, I<sub>A</sub><sup>2</sup>, I<sub>A</sub><sup>3</sup> or I<sub>A</sub><sup>17</sup> is composed, for example, of the group CO and the branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl radicals described above for R<sub>A</sub><sup>1</sup> or R<sub>A</sub><sup>2</sup>.
- 15 Optionally substituted aryl, arylalkyl or C<sub>3</sub>-C<sub>7</sub>-cycloalkyl radicals for R<sub>A</sub><sup>1</sup> or R<sub>A</sub><sup>2</sup> mean, independently of one another, for example the corresponding radicals described above for R<sub>L</sub><sup>1</sup>.
- 20 Optionally substituted hetaryl or alkylhetaryl radicals for R<sub>A</sub><sup>1</sup> or R<sub>A</sub><sup>2</sup> in the structural elements I<sub>A</sub><sup>1</sup>, I<sub>A</sub><sup>2</sup>, I<sub>A</sub><sup>3</sup> or I<sub>A</sub><sup>17</sup> mean, independently of one another, for example the corresponding radicals described above for R<sub>G</sub><sup>9</sup>.
- 25 The optionally substituted radicals CO-O-R<sub>A</sub><sup>14</sup>, O-R<sub>A</sub><sup>14</sup>, S-R<sub>A</sub><sup>14</sup>, NR<sub>A</sub><sup>15</sup>R<sub>A</sub><sup>16</sup>, CO-NR<sub>A</sub><sup>15</sup>R<sub>A</sub><sup>16</sup> or SO<sub>2</sub>NR<sub>A</sub><sup>15</sup>R<sub>A</sub><sup>16</sup> for R<sub>A</sub><sup>1</sup> or R<sub>A</sub><sup>2</sup> are composed, for example, of the groups CO-O, O, S, N, CO-N or SO<sub>2</sub>-N and the radicals R<sub>A</sub><sup>14</sup>, R<sub>A</sub><sup>15</sup> and R<sub>A</sub><sup>16</sup> which are described in detail below.
- 30 It is also possible for the two radicals R<sub>A</sub><sup>1</sup> and R<sub>A</sub><sup>2</sup> together to form a fused-on, optionally substituted, 5- or 6-membered, unsaturated or aromatic carbocyclic or heterocyclic system which may contain up to three heteroatoms selected from the group of O, N, or S.
- 35 R<sub>A</sub><sup>13</sup> and R<sub>A</sub><sup>13\*</sup> are, independently of one another, hydrogen, CN, halogen such as, for example, fluorine, chlorine, bromine or iodine,
- 40 a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl radical as described above, for example, for R<sub>A</sub><sup>1</sup> or R<sub>A</sub><sup>2</sup>, preferably methyl or trifluoromethyl or
- 45 an optionally substituted aryl, arylalkyl, hetaryl or C<sub>3</sub>-C<sub>7</sub>-cycloalkyl radical or a CO-O-R<sub>A</sub><sup>14</sup>, O-R<sub>A</sub><sup>14</sup>, S-R<sub>A</sub><sup>14</sup>, NR<sub>A</sub><sup>15</sup>R<sub>A</sub><sup>16</sup> or

CO-NR<sub>A</sub><sup>15</sup>R<sub>A</sub><sup>16</sup> radical as described in each case above for R<sub>A</sub><sup>1</sup> or R<sub>A</sub><sup>2</sup>.

A branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl or C<sub>2</sub>-C<sub>6</sub>-alkynyl radical for R<sub>A</sub><sup>14</sup> in structural element A means, for example, the corresponding radicals described above for R<sub>L</sub><sup>1</sup>.

A branched or unbranched, optionally substituted alkylene-cycloalkyl radical or alkylene-C<sub>1</sub>-C<sub>4</sub>-alkoxy radical for R<sub>A</sub><sup>14</sup> in structural element A means, for example, radicals which are composed of the branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl radicals described above for R<sub>L</sub><sup>1</sup> and of the optionally substituted C<sub>3</sub>-C<sub>7</sub>-cycloalkyl radicals or C<sub>1</sub>-C<sub>4</sub>-alkoxy radicals.

Optionally substituted aryl, arylalkyl, hetaryl or alkylhetaryl radicals for R<sub>A</sub><sup>14</sup> in structural element A mean, for example, the corresponding radicals described above for R<sub>A</sub><sup>1</sup> or R<sub>A</sub><sup>2</sup>.

A branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl or arylalkyl radical or an optionally substituted C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, aryl, hetaryl or hetarylalkyl radical for R<sub>A</sub><sup>15</sup> or R<sub>A</sub><sup>16</sup> means, independently of one another, for example the corresponding radicals described above for R<sub>A</sub><sup>14</sup>.

The branched or unbranched, optionally substituted CO-C<sub>1</sub>-C<sub>6</sub>-alkyl, SO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub>-alkyl, COO-C<sub>1</sub>-C<sub>6</sub>-alkyl, COO-alkylene-aryl or SO<sub>2</sub>-alkylene-aryl radicals or the optionally substituted CO-aryl, SO<sub>2</sub>-aryl or CO-hetaryl radicals for R<sub>A</sub><sup>15</sup> or R<sub>A</sub><sup>16</sup> are composed, for example, of the corresponding groups -CO-, -SO<sub>2</sub>-, -COO- and the corresponding branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl or arylalkyl radicals described above or the corresponding optionally substituted aryl or hetaryl radicals.

A -(CH<sub>2</sub>)<sub>n</sub>-(X<sub>A</sub>)<sub>j</sub>-R<sub>A</sub><sup>12</sup> radical for R<sub>A</sub><sup>3</sup> or R<sub>A</sub><sup>4</sup> means, independently of one another, a radical composed of the corresponding radicals -(CH<sub>2</sub>)<sub>n</sub>-, (X<sub>A</sub>)<sub>i</sub> and R<sub>A</sub><sup>12</sup>. In these cases, n can be 0, 1, 2 or 3 and j can be 0 or 1.

X<sub>A</sub> is a doubly linked radical selected from the group of -SO<sub>2</sub>-, -S-, -O-, -CO-, -O-CO-, -CO-O-, -CO-N(R<sub>A</sub><sup>12</sup>)-, -N(R<sub>A</sub><sup>12</sup>)-CO-, -N(R<sub>A</sub><sup>12</sup>)-SO<sub>2</sub>- and -SO<sub>2</sub>-N(R<sub>A</sub><sup>12</sup>)-.

R<sub>A</sub><sup>12</sup> is hydrogen,

a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl or C<sub>1</sub>-C<sub>4</sub>-alkoxy as described above for R<sub>1</sub><sup>1</sup>,

an optionally substituted -O-alkylene-aryl or -O-aryl radical,  
5 where the arylalkyl and aryl radicals have, for example, the  
meaning described above for  $R_1$  and may optionally be substituted,

an amino radical with primary or, where appropriate, secondary or tertiary substitution, such as, for example,  $\text{-NH}_2$ ,

10 -NH(C<sub>1</sub>-C<sub>6</sub>-alkyl) or -N(C<sub>1</sub>-C<sub>6</sub>-alkyl)<sub>2</sub> or, in the case of a  
terminal, singly bonded radical R<sub>A</sub><sup>12</sup>, also for example the  
corresponding cyclic amines such as, for example, N-pyrrolidinyl,  
N-piperidinyl, N-hexahydroazepinyl, N-morpholinyl or  
N-piperazinyl, and in the case where heterocycles carry free  
15 amine protons, such as, for example, N-piperazinyl, the free  
amine protons can be replaced by conventional amine protective  
groups such as, for example, methyl, benzyl, boc  
(tert-butoxycarbonyl), Z (benzyloxycarbonyl), tosyl,  
-SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub>-alkyl, -SO<sub>2</sub>-phenyl or -SO<sub>2</sub>-benzyl,

20 an optionally C<sub>1</sub>-C<sub>4</sub>-alkyl- or aryl-substituted C<sub>2</sub>-C<sub>6</sub>-alkynyl or C<sub>2</sub>-C<sub>6</sub>-alkenyl radical as described above, for example, for R<sub>L</sub><sup>1</sup>,

or a 3- to 6-membered, saturated or unsaturated heterocyclic system which is substituted by up to three identical or different radicals and which may contain up to three different or identical heteroatoms O, N, S, such as, for example, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-furyl, 3-furyl, 2-pyrrolyl, 3-pyrrolyl, 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-pyrimidyl, 4-pyrimidyl, 5-pyrimidyl, 6-pyrimidyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 1,3,4-thiadiazol-2-yl, 1,3,4-oxadiazol-2-yl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, triazinyl.

Th various radicals may form a fused-on system as generally described above.

40 C<sub>3</sub>-C<sub>7</sub>-Cycloalkyl, aryl or hetaryl radical as described above, for  
example, for R<sub>A</sub><sup>13</sup>, it being possible for two radicals together to  
be a fused-on, saturated, unsaturated or aromatic carbocyclic or  
heterocyclic system which may contain up to three different or  
45 identical heteroatoms O, N, S, and the ring may optionally be

substituted, or another, optionally substituted, saturated, unsaturated or aromatic ring may be fused onto this ring.

$R_A^3$  and  $R_A^4$  may also together form a 3- to 8-membered, saturated, 5 unsaturated or aromatic N heterocyclic system which may additionally contain two other, identical or different heteroatoms O, N or S, it being possible for the ring optionally to be substituted or for another, optionally substituted, saturated, unsaturated or aromatic ring to be fused onto this 10 ring.

$R_A^5$  is a branched or unbranched, optionally substituted  $C_1$ - $C_6$ -alkyl, arylalkyl or  $C_3$ - $C_7$ -cycloalkyl radical as described above, for example, for  $R_L^1$ , or a  $C_1$ - $C_6$ -alkyl- $C_3$ - $C_7$ -cycloalkyl 15 radical which is composed, for example, of the corresponding radicals described above.

$R_A^6$  and  $R_A^{6*}$  are, independently of one another, hydrogen, a branched or unbranched, optionally substituted  $C_1$ - $C_4$ -alkyl radical 20 such as, for example, optionally substituted methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl,

-CO-O- $C_1$ - $C_4$ -alkyl or -CO- $C_1$ - $C_4$ -alkyl radical such as, for example, 25 composed of the group -CO-O- or -CO- and the  $C_1$ - $C_4$ -alkyl radicals described above,

arylalkyl radical as described above for  $R_L^1$ ,

30 -CO-O-alkylene-aryl or -CO-alkylene-aryl radical such as, for example, composed of the group -CO-O- or -CO- and the arylalkyl radicals described above,

-CO-O-allyl or -CO-allyl radical, 35

or  $C_3$ - $C_7$ -cycloalkyl radical as described above, for example, for  $R_L^1$ .

It is also possible for the two radicals  $R_A^6$  and  $R_A^{6*}$  in 40 structural element  $I_A^7$  together to form an optionally substituted, saturated, unsaturated or aromatic heterocyclic system which, in addition to the ring nitrogen, may contain up to two other different or identical heteroatoms O, N, S.

45  $R_A^7$  is hydrogen, -OH, -CN, -CONH<sub>2</sub>, a branched or unbranched, optionally substituted  $C_1$ - $C_4$ -alkyl radical, for example as described above for  $R_A^6$ ,  $C_1$ - $C_4$ -alkoxy, arylalkyl or



- C<sub>3</sub>-C<sub>7</sub>-cycloalkyl radical, for example as described above for R<sub>L</sub><sup>1</sup>, a branched or unbranched, optionally substituted -O-CO-C<sub>1</sub>-C<sub>4</sub>-alkyl radical which is composed of the group -O-CO- and, for example, of the abovementioned C<sub>1</sub>-C<sub>4</sub>-alkyl radicals, or an optionally substituted -O-alkylene-aryl, -O-CO-aryl, -O-CO-alkylene-aryl or -O-CO-allyl radical which is composed of the groups -O- or -O-CO- and, for example, of the corresponding radicals described above for R<sub>L</sub><sup>1</sup>.
- 10 It is also possible for the two radicals R<sub>A</sub><sup>6</sup> and R<sub>A</sub><sup>7</sup> together to form an optionally substituted, unsaturated or aromatic heterocyclic system which, in addition to the ring nitrogen, may contain up to two other different or identical heteroatoms O, N, S.
- 15 A branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>4</sub>-alkyl radical or an optionally substituted aryl or arylalkyl radical for R<sub>A</sub><sup>8</sup> in structural element A means, for example, the corresponding radicals described above for R<sub>A</sub><sup>15</sup>, where the
- 20 CO-C<sub>1</sub>-C<sub>4</sub>-alkyl, SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub>-alkyl, CO-O-C<sub>1</sub>-C<sub>4</sub>-alkyl, CO-aryl, SO<sub>2</sub>-aryl, CO-O-aryl, CO-alkylene-aryl, SO<sub>2</sub>-alkylene-aryl or CO-O-alkylene-aryl radicals are composed, in analogy to the other composed radicals, of the group CO, SO<sub>2</sub> or COO and, for example, of the corresponding C<sub>1</sub>-C<sub>4</sub>-alkyl, aryl or arylalkyl radicals
- 25 described above for R<sub>A</sub><sup>15</sup>, and these radicals may optionally be substituted.
- Halogen for R<sub>A</sub><sup>9</sup> or R<sub>A</sub><sup>10</sup> means, independently of one another, fluorine, chlorine, bromine or iodine.
- 30 A branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl radical or an optionally substituted aryl, arylalkyl, hetaryl or C<sub>3</sub>-C<sub>7</sub>-cycloalkyl radical in each case for R<sub>A</sub><sup>9</sup> or R<sub>A</sub><sup>10</sup> mean, independently of one another, for example the corresponding
- 35 radicals described above for R<sub>A</sub><sup>14</sup>, preferably methyl or trifluoromethyl.
- A CO-O-R<sub>A</sub><sup>14</sup>, O-R<sub>A</sub><sup>14</sup>, S-R<sub>A</sub><sup>14</sup>, NR<sub>A</sub><sup>15</sup>R<sub>A</sub><sup>16</sup> or CO-NR<sub>A</sub><sup>15</sup>R<sub>A</sub><sup>16</sup> radical in each case for R<sub>A</sub><sup>9</sup> or R<sub>A</sub><sup>10</sup> means, independently of one another, for
- 40 example the corresponding radicals described above for R<sub>A</sub><sup>13</sup>.
- It is also possible for the two radicals R<sub>A</sub><sup>9</sup> and R<sub>A</sub><sup>10</sup> together in the structural element I<sub>A</sub><sup>14</sup> to form a 5- to 7-membered saturated, unsaturated or aromatic carbocyclic or heterocyclic system which
- 45 may contain up to three different or identical heteroatoms O, N,

S and is optionally substituted by up to three identical or different radicals.

Substituents mean in this case in particular halogen, CN, a  
 5 branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>4</sub>-alkyl radical such as, for example, methyl or trifluoromethyl or the radicals O-R<sub>A</sub><sup>14</sup>, S-R<sub>A</sub><sup>14</sup>, NR<sub>A</sub><sup>15</sup>R<sub>A</sub><sup>16</sup>, CO-NR<sub>A</sub><sup>15</sup>R<sub>A</sub><sup>16</sup> or -((R<sub>A</sub><sup>8</sup>)HN)C=N-R<sub>A</sub><sup>7</sup>.

Halogen for R<sub>A</sub><sup>11</sup> means, for example, fluorine, chlorine, bromine  
 10 or iodine.

A branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl radical or an optionally substituted aryl, arylalkyl, hetaryl, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl radical or a CO-O-R<sub>A</sub><sup>14</sup>, O-R<sub>A</sub><sup>14</sup>, S-R<sub>A</sub><sup>14</sup>, NR<sub>A</sub><sup>15</sup>R<sub>A</sub><sup>16</sup> or  
 15 CO-NR<sub>A</sub><sup>15</sup>R<sub>A</sub><sup>16</sup> radical for R<sub>A</sub><sup>11</sup> means, for example, the corresponding radicals described above for R<sub>A</sub><sup>9</sup>.

It is also possible for the two radicals R<sub>A</sub><sup>9</sup> and R<sub>A</sub><sup>17</sup> in the structural element I<sub>A</sub><sup>16</sup> together to form a 5- to 7-membered  
 20 saturated, unsaturated or aromatic heterocyclic system which may, in addition to the ring nitrogen, contain up to three different or identical heteroatoms O, N, S and is optionally substituted by up to three identical or different radicals.

Z<sup>1</sup>, Z<sup>2</sup>, Z<sup>3</sup>, Z<sup>4</sup> are, independently of one another, nitrogen, C-H, C-halogen such as, for example, C-F, C-Cl, C-Br or C-I or a branched or unbranched, optionally substituted C-C<sub>1</sub>-C<sub>4</sub>-alkyl radical which is composed of a carbon radical and, for example, a C<sub>1</sub>-C<sub>4</sub>-alkyl radical described above for R<sub>A</sub><sup>6</sup>, or a branched or  
 30 unbranched, optionally substituted C-C<sub>1</sub>-C<sub>4</sub>-alkoxy radical which is composed of a carbon radical and, for example, a C<sub>1</sub>-C<sub>4</sub>-alkoxy radical described above for R<sub>A</sub><sup>7</sup>.

Z<sup>5</sup> is oxygen, sulfur or an NR<sub>A</sub><sup>8</sup> radical.

35 Preferred structural elements A are composed of the preferred radicals of the structural element.

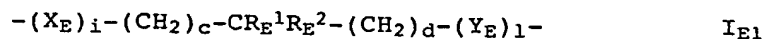
Particularly preferred structural elements A are composed of the  
 40 particularly preferred radicals of the structural element.

In a preferred embodiment, the spacer structural element E means a structural element which consists of a branched or unbranched, optionally substituted and heteroatom-containing aliphatic  
 45 C<sub>2</sub>-C<sub>30</sub>-hydrocarbon radical and/or of a 4- to 20-membered,

optionally substituted and heteroatom-containing, aliphatic or aromatic mono- or polycyclic hydrocarbon radical.

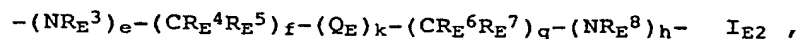
In a particularly preferred embodiment, the spacer structural element E is composed of two to four partial structural elements selected from the group of E<sup>1</sup> and E<sup>2</sup> together, the partial structural elements being linked in any sequence, and E<sup>1</sup> and E<sup>2</sup> having the following meanings:

10 E<sup>1</sup> a partial structural element of the formula I<sub>E1</sub>



and

15 E<sup>2</sup> a partial structural element of the formula I<sub>E2</sub>



20 where

c, d, f, g  
are, independently of one another, 0, 1 or 2,

25 e, h, i, k, l,  
are, independently of one another, 0 or 1,

X<sub>E</sub>, Q<sub>E</sub>

30 are, independently of one another, CO, CO-NR<sub>E</sub><sup>9</sup>, S, SO, SO<sub>2</sub>, SO<sub>2</sub>NR<sub>E</sub><sup>9</sup>, CS, CS-NR<sub>E</sub><sup>9</sup>, CS-O, CO-O, O-CO, O, ethynyl, CR<sub>E</sub><sup>10</sup>-O-CR<sub>E</sub><sup>11</sup>, CR<sub>E</sub><sup>10</sup>R<sub>E</sub><sup>11</sup>, C(=CR<sub>E</sub><sup>10</sup>R<sub>E</sub><sup>11</sup>), CR<sub>E</sub><sup>10</sup>=CR<sub>E</sub><sup>11</sup>, CR<sub>E</sub><sup>10</sup>(OR<sub>E</sub><sup>12</sup>)-CR<sub>E</sub><sup>11</sup>, CR<sub>E</sub><sup>10</sup>-CR<sub>E</sub><sup>11</sup>(OR<sub>E</sub><sup>12</sup>) or an  
35 optionally substituted 4- to 11-membered mono- or polycyclic aliphatic or aromatic hydrocarbon which may contain up to 6 double bonds and up to 6 heteroatoms selected from the group of N, O, S,

Y<sub>E</sub> is -CO-, -NR<sub>E</sub><sup>9</sup>-CO-, -SO-, -SO<sub>2</sub>-, -NR<sub>E</sub><sup>9</sup>-SO<sub>2</sub>-, -CS-,  
40 -NR<sub>E</sub><sup>9</sup>-CS-, -O-CS- or -O-CO-

45

$R_E^1, R_E^2, R_E^4, R_E^5, R_E^6, R_E^7$ 

are, independently of one another, hydrogen, halogen, a hydroxyl group, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkynyl or alkylene-cycloalkyl radical, a -(CH<sub>2</sub>)<sub>w</sub>-R<sub>E</sub><sup>13</sup> radical, an optionally substituted C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, aryl, arylalkyl, hetaryl, hetarylalkyl, O-aryl or O-alkylene-aryl radical, or, independently of one another, in each case two radicals R<sub>E</sub><sup>1</sup> and R<sub>E</sub><sup>2</sup> or R<sub>E</sub><sup>4</sup> and R<sub>E</sub><sup>5</sup> or R<sub>E</sub><sup>6</sup> and R<sub>E</sub><sup>7</sup> together are a 3- to 7-membered, optionally substituted, saturated or unsaturated carbocyclic system.

15

where

w is 0, 1, 2, 3 or 4,

 $R_E^3, R_E^8, R_E^9$ 

20

are, independently of one another, hydrogen, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl, CO-C<sub>1</sub>-C<sub>6</sub>-alkyl, CO-O-C<sub>1</sub>-C<sub>6</sub>-alkyl or SO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub>-alkyl radical or an optionally substituted C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, CO-O-alkylene-aryl, CO-alkylene-aryl, CO-aryl, SO<sub>2</sub>-aryl, CO-hetaryl or SO<sub>2</sub>-alkylene-aryl radical.

25

 $R_E^{10}, R_E^{11}$ 

30

are, independently of one another, hydrogen, a hydroxyl group, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkynyl or alkylene-cycloalkyl radical or an optionally substituted C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, aryl, arylalkyl, hetaryl or hetarylalkyl radical,

35

R<sub>E</sub><sup>12</sup> is hydrogen, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkynyl or alkylene-cycloalkyl radical or an optionally substituted C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, aryl, arylalkyl, hetaryl or hetarylalkyl radical,

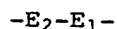
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45

30  
 $R_E^{13}$  is hydrogen, a hydroxyl group, a branched or unbranched, optionally substituted  $C_1$ - $C_6$ -alkyl,  $C_1$ - $C_4$ -alkoxy, -arylalkyl, -O-alkylene-aryl or -O-aryl radical, an amino radical with primary or, where appropriate, secondary or tertiary substitution, an optionally  $C_1$ - $C_4$ -alkyl- or aryl-substituted  $C_2$ - $C_6$ -alkynyl or  $C_2$ - $C_6$ -alkenyl radical, a  $C_5$ - $C_{12}$ -bicycloalkyl,  $C_6$ - $C_{18}$ -tricycloalkyl radical, a CO-O- $R_A^{14}$  radical, or a 3- to 6-membered, saturated or unsaturated heterocyclic system which is substituted by up to three identical or different radicals and which may contain up to three different or identical heteroatoms O, N, S,  $C_3$ - $C_7$ -cycloalkyl, aryl or hetaryl radical, it being possible for two radicals together to be a fused-on, saturated, unsaturated or aromatic carbocyclic or heterocyclic system which may contain up to three different or identical heteroatoms O, N, S, and the ring may optionally be substituted or another, optionally substituted, saturated, unsaturated or aromatic ring may be fused onto this ring.

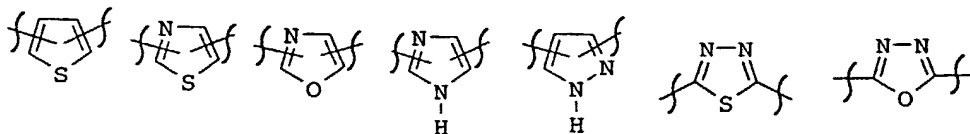
In an even more preferred embodiment, the spacer structural element E used is a structural element of the formula  $I_{E1E2}$

25

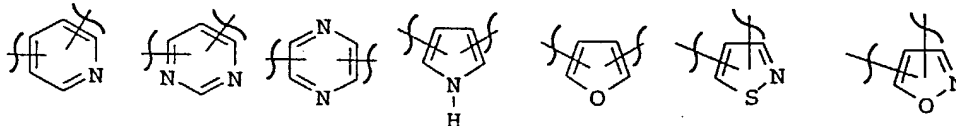


An optionally substituted 4- to 11-membered mono- or polycyclic aliphatic or aromatic hydrocarbon which may contain up to 6 double bonds and up to 6 heteroatoms selected from the group of N, O, S for  $Q_E$  and  $X_E$  mean, independently of one another, preferably optionally substituted aryl such as, for example, optionally substituted phenyl or naphthyl, optionally substituted hetaryl such as, for example, the radicals

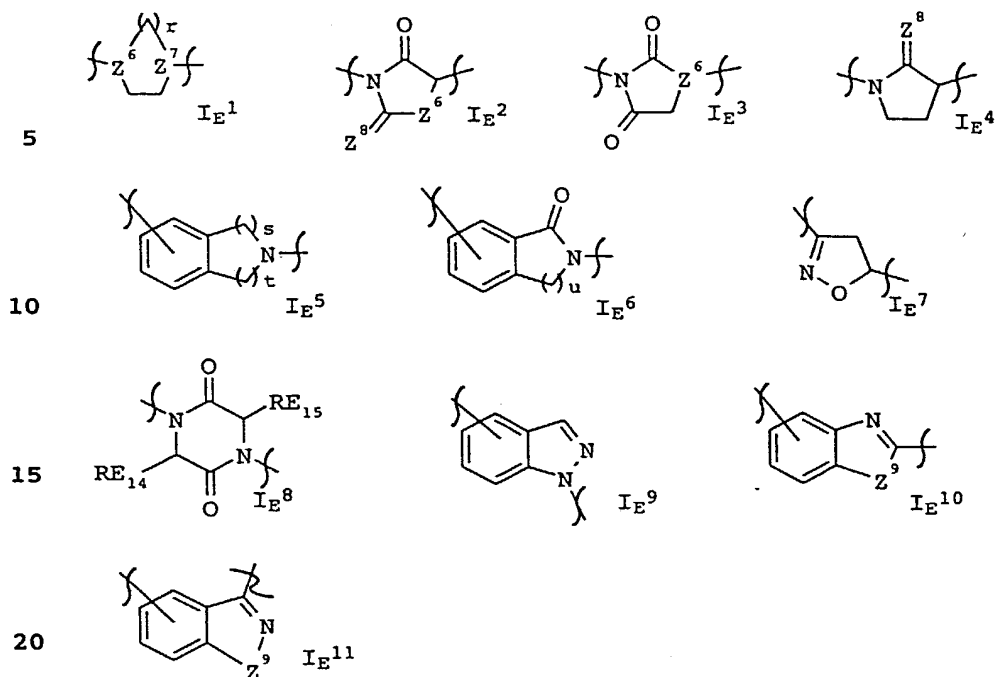
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40



45 and their substituted derivatives, or radicals of the formulae  $I_E^1$  to  $I_E^{11}$



it being possible for the radicals to be incorporated in both  
25 orientations.

$Z^6$  and  $Z^7$  are, independently of one another, CH or nitrogen.

$Z^8$  is oxygen, sulfur or NH.

30

$Z^9$  is oxygen, sulfur or  $NR_E^{16}$ .

r and t are, independently of one another, 0, 1, 2 or 3.

35 s and u are, independently of one another, 0, 1 or 2.

$R_E^{14}$  and  $R_E^{15}$  are, independently of one another, hydrogen,  $-NO_2$ ,  $-NH_2$ ,  $-CN$ ,  $-COOH$ , a hydroxyl group, halogen, a branched or unbranched, optionally substituted  $C_1$ - $C_6$ -alkyl,  $C_1$ - $C_4$ -alkoxy,  
40  $C_2$ - $C_6$ -alkenyl,  $C_2$ - $C_6$ -alkynyl or alkylene-cycloalkyl radical or an optionally substituted cycloalkyl, aryl, arylalkyl, hetaryl or hetarylalkyl radical as described above in each case.

$R_E^{16}$  means, independently of one another, hydrogen, a branched or  
45 unbranched, optionally substituted  $C_1$ - $C_6$ -alkyl,  $C_1$ - $C_6$ -alkoxyalkyl,  $C_3$ - $C_{12}$ -alkynyl,  $CO$ - $C_1$ - $C_6$ -alkyl,  $CO$ - $O$ - $C_1$ - $C_6$ -alkyl or  $SO_2$ - $C_1$ - $C_6$ -alkyl radical or an optionally substituted  $C_3$ - $C_7$ -cycloalkyl, aryl,

arylalkyl, CO-O-alkylene-aryl, CO-alkylene-aryl, CO-aryl, SO<sub>2</sub>-aryl, hetaryl, CO-hetaryl or SO<sub>2</sub>-alkylene-aryl radical, preferably hydrogen or a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl radical.

5

Preferred radicals for Q<sub>E</sub> are the radicals CO, CO-NR<sub>E</sub><sup>9</sup>, S, SO, SO<sub>2</sub>, SO<sub>2</sub>NR<sub>E</sub><sup>9</sup>, CS, CS-NR<sub>E</sub><sup>9</sup>, CS-O, CO-O, O-CO, O, ethynyl, CR<sub>E</sub><sup>10</sup>-O-CR<sub>E</sub><sup>11</sup>, CR<sub>E</sub><sup>10</sup>R<sub>E</sub><sup>11</sup>, C(=CR<sub>E</sub><sup>10</sup>R<sub>E</sub><sup>11</sup>), CR<sub>E</sub><sup>10</sup>=CR<sub>E</sub><sup>11</sup>, CR<sub>E</sub><sup>10</sup>(OR<sub>E</sub><sup>12</sup>)-CR<sub>E</sub><sup>11</sup>, CR<sub>E</sub><sup>10</sup>-CR<sub>E</sub><sup>11</sup>(OR<sub>E</sub><sup>12</sup>), substituted aryl or hetaryl

10 as described above, or the radicals of the formulae I<sub>E</sub><sup>1</sup> to I<sub>E</sub><sup>11</sup>.

Particularly preferred radicals for Q<sub>E</sub> are the radicals CO, CO-NR<sub>E</sub><sup>9</sup>, S, SO, SO<sub>2</sub>, SO<sub>2</sub>NR<sub>E</sub><sup>9</sup>, CS, CS-NR<sub>E</sub><sup>9</sup>, CS-O, CO-O, O-CO, O, ethynyl, CR<sub>E</sub><sup>10</sup>-O-CR<sub>E</sub><sup>11</sup>, CR<sub>E</sub><sup>10</sup>R<sub>E</sub><sup>11</sup>, C(=CR<sub>E</sub><sup>10</sup>R<sub>E</sub><sup>11</sup>), CR<sub>E</sub><sup>10</sup>=CR<sub>E</sub><sup>11</sup>,  
 15 CR<sub>E</sub><sup>10</sup>(OR<sub>E</sub><sup>12</sup>)-CR<sub>E</sub><sup>11</sup>, CR<sub>E</sub><sup>10</sup>-CR<sub>E</sub><sup>11</sup>(OR<sub>E</sub><sup>12</sup>), substituted aryl or hetaryl as described above, or the radicals of the formulae I<sub>E</sub><sup>1</sup>, I<sub>E</sub><sup>4</sup>, I<sub>E</sub><sup>6</sup>, I<sub>E</sub><sup>7</sup>, I<sub>E</sub><sup>9</sup> or I<sub>E</sub><sup>10</sup>.

Preferred radicals for X<sub>E</sub> are the radicals CO, CO-NR<sub>E</sub><sup>9</sup>, S, SO<sub>2</sub>NR<sub>E</sub><sup>9</sup>,  
 20 CS, CS-NR<sub>E</sub><sup>9</sup>, CO-O, O-CO, O, ethynyl, CR<sub>E</sub><sup>10</sup>-O-CR<sub>E</sub><sup>11</sup>, CR<sub>E</sub><sup>10</sup>R<sub>E</sub><sup>11</sup> or CR<sub>E</sub><sup>10</sup>=CR<sub>E</sub><sup>11</sup>, particularly preferably CO, CO-NR<sub>E</sub><sup>9</sup>, SO<sub>2</sub>NR<sub>E</sub><sup>9</sup>, O, ethynyl, CR<sub>E</sub><sup>10</sup>-O-CR<sub>E</sub><sup>11</sup> or CR<sub>E</sub><sup>10</sup>R<sub>E</sub><sup>11</sup>.

Preferred radicals for R<sub>E</sub><sup>1</sup> are hydrogen, fluorine, chlorine or a  
 25 -(CH<sub>2</sub>)<sub>w</sub>-R<sub>E</sub><sup>13</sup> radical, where w is 0, 1, 2, 3 or 4.

Preferred radicals for R<sub>E</sub><sup>2</sup> are hydrogen, halogen, particularly preferably chlorine or fluorine, a hydroxyl group or a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl or C<sub>1</sub>-C<sub>4</sub>-alkoxy  
 30 radical, particularly preferably methyl or ethyl.

In a further preferred embodiment, the two radicals R<sub>E</sub><sup>1</sup> and R<sub>E</sub><sup>2</sup> together form a 3- to 7-membered, optionally substituted, saturated, unsaturated or aromatic carbocyclic system.

35

The preferred and particularly preferred radicals for R<sub>E</sub><sup>4</sup> and R<sub>E</sub><sup>6</sup> and for R<sub>E</sub><sup>5</sup> and R<sub>E</sub><sup>7</sup> are, independently of one another, in each case the corresponding radicals which are the same as mentioned above for R<sub>E</sub><sup>1</sup> and R<sub>E</sub><sup>2</sup>.

40

It is once again possible, in a preferred embodiment, for the radicals R<sub>E</sub><sup>4</sup> and R<sub>E</sub><sup>5</sup> or R<sub>E</sub><sup>6</sup> and R<sub>E</sub><sup>7</sup> together to form a 3- to 7-membered, optionally substituted carbocyclic system in this case.

45

Preferred radicals for  $R_E^3$  are hydrogen or a branched or unbranched, optionally substituted  $C_1$ - $C_6$ -alkyl radical, particularly preferably methyl.

- 5 Preferred radicals for  $R_E^8$  and  $R_E^9$  are, independently of one another, hydrogen, a branched or unbranched, optionally substituted  $C_1$ - $C_4$ -alkyl,  $C_3$ - $C_7$ -cycloalkyl, CO- $C_1$ - $C_4$ -alkyl, CO-O-alkylene-aryl, particularly preferably CO-O-benzyl, CO-alkylene-aryl, particularly preferably CO-phenyl,  
 10 CO-O- $C_1$ - $C_4$ -alkyl,  $SO_2$ - $C_1$ - $C_4$ -alkyl,  $SO_2$ -aryl, particularly preferably tosyl or  $SO_2$ -alkylene-aryl radical.

- Preferred radicals for  $R_E^{10}$  and  $R_E^{11}$  are, independently of one another, hydrogen, a hydroxyl group, a branched or unbranched,  
 15 optionally substituted  $C_1$ - $C_6$ -alkyl, particularly preferably  $C_1$ - $C_4$ -alkyl, or  $C_1$ - $C_4$ -alkoxy radical or an optionally substituted aryl, arylalkyl, hetaryl or hetarylalkyl radical.

- Preferred radicals for  $R_E^{12}$  are, independently of one another,  
 20 hydrogen, a branched or unbranched, optionally substituted  $C_1$ - $C_6$ -alkyl radical or an optionally substituted arylalkyl or hetarylalkyl radical.

- A branched or unbranched  $C_1$ - $C_6$ -alkyl radical for  $R_E^{13}$  means, for  
 25 example, methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl,  
 30 2,3-dimethylbutyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethylbutyl, 2-ethylbutyl or 1-ethyl-2-methylpropyl, preferably methyl, ethyl, propyl, butyl, isopropyl, sec-butyl and tert-butyl.

- 35 A branched or unbranched  $C_1$ - $C_4$ -alkoxy radical for  $R_E^{13}$  means, for example, methoxy, ethoxy, propoxy, 1-methylethoxy, butoxy, 1-methylpropoxy, 2-methylpropoxy or 1,1-dimethylethoxy, in particular methoxy, ethoxy or 1-methylethoxy.

- 40 Examples of -O-alkylene-aryl or -O-aryl radicals are -O-phenyl, -O-1-naphthyl, -O-2-naphthyl or -O-benzyl.

- The  $C_1$ - $C_6$ -alkyl and  $C_1$ - $C_4$ -alkoxy radicals of  $R_E^{13}$  may be  
 45 substituted by up to five identical or different substituents as described at the outset.



Substituted -O-alkylene-aryl or -O-aryl radicals mean, for example, the abovementioned -O-alkylene-aryl or -O-aryl radicals, it being possible for the aryl moiety to be substituted by up to three identical or different substituents as described at the 5 outset.

An amino radical with primary or, where appropriate, secondary or tertiary substitution for  $R_E^{13}$  in structural element I means a primary amino radical  $-NH_2$ , a secondary amino radical  $-NH(R_E^{131})$  10 or a tertiary amino radical  $-N(R_E^{131})(R_E^{132})$ , where

$R_E^{131}$  and  $R_E^{132}$  can be, independently of one another,  $C_1$ - $C_4$ -alkyl or  $C_3$ - $C_6$ -cycloalkyl as mentioned above, optionally substituted aryl, preferably phenyl, arylalkyl, preferably benzyl, 15 - $CO$ - $C_1$ - $C_4$ -alkyl, preferably - $CO$ - $CH_3$  or - $CO$ -aryl, preferably - $CO$ -phenyl.

Cyclic amino radicals result in the case where  $R_E^{13}$  is one of the heterocycles described below, which is bonded via the ring 20 nitrogen.

An optionally  $C_1$ - $C_4$ -alkyl- or aryl-substituted  $C_2$ - $C_6$ -alkynyl or  $C_2$ - $C_6$ -alkenyl radical for  $R_E^{13}$  means, for example,  $C_2$ - $C_6$ -alkynyl radicals such as, for example, ethynyl, 2-propynyl, 2-butyne, 25 3-butyne, 1-methyl-2-propynyl, 2-pentyne, 3-pentyne, 4-pentyne, 1-methyl-3-butyne, 2-methyl-3-butyne, 1-methyl-2-butyne, 1,1-dimethyl-2-propynyl, 1-ethyl-2-propynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 1-methyl-2-pentyne, 1-methyl-3-pentyne, 1-methyl-4-pentyne, 2-methyl-3-pentyne, 30 2-methyl-4-pentyne, 3-methyl-4-pentyne, 4-methyl-2-pentyne, 1,1-dimethyl-2-butyne, 1,1-dimethyl-3-butyne, 1,2-dimethyl-3-butyne, 2,2-dimethyl-3-butyne, 1-ethyl-2-butyne, 1-ethyl-3-butyne, 2-ethyl-3-butyne or 1-ethyl-1-methyl-2-propynyl, preferably 2-propynyl or ethynyl 35

or  $C_2$ - $C_6$ -alkenyl radical, such as, for example, vinyl, 2-propenyl, 2-butenyl, 3-butenyl, 1-methyl-2-propenyl, 2-methyl-2-propenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-methyl-2-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 1-methyl-3-butenyl, 2-methyl-3- 40 butenyl, 3-methyl-3-butenyl, 1,1-dimethyl-2-propenyl, 1,2-dimethyl-2-propenyl, 1-ethyl-2-propenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 1-methyl-2-pentenyl, 2-methyl-2-pentenyl, 3-methyl-2-pentenyl, 4-methyl-2-pentenyl, 3-methyl-3-pentenyl, 4-methyl-3-pentenyl, 1-methyl-4-pentenyl, 45 2-methyl-4-pentenyl, 3-methyl-4-pentenyl, 4-methyl-4-pentenyl, 1,1-dimethyl-2-butenyl, 1,1-dimethyl-3-butenyl, 1,2-dimethyl-2-butenyl, 1,2-dimethyl-3-butenyl,

1,3-dimethyl-2-butenyl, 1,3-dimethyl-3-butenyl,  
2,2-dimethyl-3-butenyl, 2,3-dimethyl-2-butenyl,  
2,3-dimethyl-3-butenyl, 1-ethyl-2-butenyl, 1-ethyl-3-butenyl,  
2-ethyl-2-butenyl, 2-ethyl-3-butenyl, 1,1,2-trimethyl-2-propenyl,  
5 1-ethyl-1-methyl-2-propenyl or 1-ethyl-2-methyl-2-propenyl, in  
particular 2-propenyl or vinyl,

each of which may be substituted by optionally substituted  
C<sub>1</sub>-C<sub>4</sub>-alkyl radicals or aryl radicals as mentioned above,  
10 preferably phenyl, such as, preferably, phenylethynyl or  
phenylethenyl.

A C<sub>5</sub>-C<sub>12</sub>-bicycloalkyl radical for R<sub>E</sub><sup>13</sup> means, for example, indanyl,  
norbornyl or camphyl, and a C<sub>6</sub>-C<sub>18</sub>-tricycloalkyl radical means,  
15 for example, adamantyl.

The CO-O-R<sub>A</sub><sup>14</sup> radical is composed, as mentioned above several  
times, of the group CO-O and the R<sub>A</sub><sup>14</sup> radical described above for  
structural element A.

20

A 3- to 6-membered, saturated or unsaturated heterocyclic system  
which is substituted by up to three identical or different  
radicals and may contain up to three different or identical  
heteroatoms O, N, S, or C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, aryl or heteroaryl  
25 radical, it being possible for two radicals together to be a  
fused-on, 3- to 7-membered, saturated, unsaturated or aromatic  
carbocyclic or heterocyclic system which may contain up to three  
different or identical heteroatoms O, N, S, and the ring can  
optionally be substituted, or another, optionally substituted,  
30 saturated, unsaturated or aromatic ring may be fused onto this  
ring, for R<sub>E</sub><sup>13</sup> means, for example,

3- to 6-membered, saturated or unsaturated heterocycles which may  
contain up to three different or identical heteroatoms O, N, S,  
35 such as N-pyrrolidinyl, N-piperidinyl, N-hexahydroazepinyl,  
N-morpholinyl or N-piperazinyl, and in the case of heterocycles  
which have free amine protons, such as, for example,  
N-piperazinyl, the free amine protons may be replaced by  
conventional amine protective groups, such as, for example,  
40 methyl, benzyl, boc (tert-butoxycarbonyl), Z (benzyloxycarbonyl),  
tosyl, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub>-alkyl, -SO<sub>2</sub>-phenyl or -SO<sub>2</sub>-benzyl,

C<sub>3</sub>-C<sub>7</sub>-cycloalkyl radicals as described above for R<sub>L</sub><sup>1</sup>,

45 aryl radicals such as, for example, phenyl, 1-naphthyl or  
2-naphthyl or

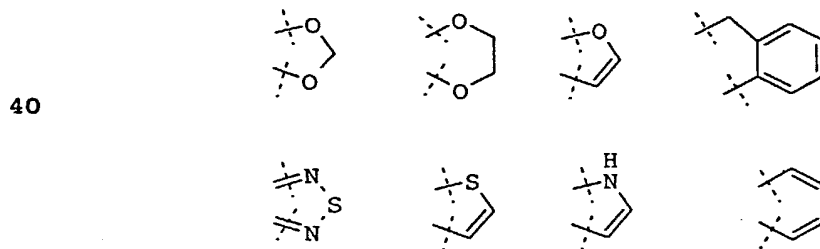
hetaryl radicals such as, for example, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-furyl, 3-furyl, 2-pyrrolyl, 3-pyrrolyl, 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-pyrimidyl, 4-pyrimidyl, 5-pyrimidyl, 5 6-pyrimidyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 1,3,4-thiadiazol-2-yl, 1,3,4-oxadiazol-2-yl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl or 10 triazinyl, preferably 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl or 5-thiazolyl,

it being possible for the heterocyclic, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, aryl and 15 heteroaryl radicals optionally to be substituted by up to three identical or different radicals.

Preferred substituents of the heterocyclic, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, aryl and hetaryl radicals for R<sub>E</sub><sup>13</sup> are C<sub>1</sub>-C<sub>4</sub>-alkyl, -COOH, -COOMe, -CF<sub>3</sub>, 20 -CN, C<sub>1</sub>-C<sub>4</sub>-alkoxy, -SCH<sub>3</sub>, -O-CH<sub>2</sub>-COOH, -phenyl, -SO<sub>2</sub>CH<sub>3</sub>, -NO<sub>2</sub>, -OH, -NH<sub>2</sub>, -N-pyrrolidinyl, -N-piperidinyl, -N-morpholinyl, -N-piperazinyl, -NH-C<sub>1</sub>-C<sub>4</sub>-alkyl, -N(C<sub>1</sub>-C<sub>4</sub>-alkyl)<sub>2</sub>, F, Cl, Br or I.

With the hetaryl radicals it is also possible for two radicals 25 together to form, as described above generally, a fused-on system.

Preferred substituents of the heterocyclic, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, aryl and hetaryl radicals for R<sub>E</sub><sup>13</sup> in which two radicals together are a 30 fused-on, saturated, unsaturated or aromatic carbocyclic or heterocyclic system which may contain up to three different or identical heteroatoms O, N, S, and the ring may optionally be substituted or another, optionally substituted ring may be fused onto this ring, are the following doubly linked structural 35 elements:



Examples of the resulting fused cyclic systems for  $R_E^{13}$  are, for example, the corresponding dioxolanyls, benzopyrrolyls, benzofuryls, benzothienyls or fluorenyls.

- 5 Preferred structural elements E are composed of the preferred radicals for structural element E.

Preferred structural elements B are composed of the preferred structural elements A and E.

10

The compounds of the formula I and the intermediates for their preparation may have one or more asymmetric substituted carbon atoms. The compounds may be in the form of pure enantiomers or pure diastereomers or a mixture thereof. The use of an

- 15 enantiomerically pure compound as active ingredient is preferred.

The compounds of the formula I may also be in the form of physiologically tolerated salts.

- 20 The compounds of the formula I may also be in the form of prodrugs where the compounds of the formula I are released under physiological conditions. Reference may be made in this connection by way of example to group T in structural element L, which group contains some groups which can be hydrolyzed under  
25 physiological conditions to the free carboxyl group. Also suitable are derivatized structural elements B or A which release the structural element B or A under physiological conditions.

- In preferred compounds of the formula I, in each case one of the  
30 three structural elements B, G or L has the preferred range, while the remaining structural elements may vary widely.

- In particularly preferred compounds of the formula I, in each case two of the three structural elements B, G or L have the  
35 preferred range, while the remaining structural elements may vary widely.

- In very particularly preferred compounds of the formula I, in each case all three structural elements B, G or L have the  
40 preferred range, while the remaining structural element may vary widely.

- Preferred compounds of the formula I have, for example, the preferred structural element G, while the structural elements B  
45 and L may vary widely.

In particularly preferred compounds of the formula I, for example, B is replaced by the structural element A-E-, and the compounds have, for example, the preferred structural element G and the preferred structural element A, while the structural elements E and L may vary widely.

Further particularly preferred compounds have, for example, the preferred structural element G and the preferred structural element A, while the structural elements E and L may vary widely.

10

Very preferred compounds of the formula I in which A-E- represents B- are listed in the following table, where "compound" represents the number of an individualized compound of the formula I, and the meaning of the abbreviations of the structural elements is explained after the table.

	Compound	Structural elements A-E-G-L
20	1	2pmhs-am2-pheac-es
	2	2pmhs-dibema2-phec-gs
	3	2pmhs-edia2-phec-es
	4	2py-25thima2-pheaz-es
	5	2py-25thima2-phec-es
25	6	2py-35thima2-pheaz-es
	7	2py-35thima2-phec-es
	8	2py-42thiaz2-pheaz-es
	9	2py-42thiaz2-phec-es
	30	10
11		2py-aaf-phec-es
12		2py-am2-8mephec-es
13		2py-am2-8mephec-gs
35		14
	15	2py-am2-deophec-es
	16	2py-am2-deophec-gs
	17	2py-am2-deophec-ps
	40	18
19		2py-am2-pheaz-ps
20		2py-am2-phec-es
21		2py-am2-phec-gs
45		22
	23	2py-am2-thioph-es
	24	2py-am2-thioph-gs
	25	2py-am2-thioph-ps

Compound	Structural elements A-E-G-L
26	2py-aof-pheaz-es
27	2py-aof-phhec-es
5 28	2py-buta-pheaz-es
29	2py-buta-phhec-es
30	2py-chex2-pheaz-es
31	2py-chex2-phhec-es
10 32	2py-dibema2-23dimephec-es
33	2py-dibema2-27dimeophec-es
34	2py-dibema2-2mephec-es
35	2py-dibema2-49dimeophec-es
36	2py-dibema2-5claz-es
15 37	2py-dibema2-69dimeophec-es
38	2py-dibema2-69dimephec-es
39	2py-dibema2-78diclphec-es
40	2py-dibema2-78dimeophec-es
20 41	2py-dibema2-8mephec-es
42	2py-dibema2-8mephec-gs
43	2py-dibema2-8mephec-ps
44	2py-dibema2-8mepyaz-es
25 45	2py-dibema2-9clphec-es
46	2py-dibema2-benz-es
47	2py-dibema2-cl2phec-es
48	2py-dibema2-deophec-es
49	2py-dibema2-deophec-gs
30 50	2py-dibema2-deophec-ps
51	2py-dibema2-deothioph-es
52	2py-dibema2-dimepy-es
53	2py-dibema2-dimepyaz-es
35 54	2py-dibema2-dimethio-es
55	2py-dibema2-dmaphec-es
56	2py-dibema2-imon-es
57	2py-dibema2-meoaz-es
40 58	2py-dibema2-meophe-es
59	2py-dibema2-meophe-nes
60	2py-dibema2-meophe-f2es
61	2py-dibema2-mephe-gs
45 62	2py-dibema2-pheaz-es
63	2py-dibema2-pheaz-ps
64	2py-dibema2-phhec-es

	Compound	Structural elements A-E-G-L
5	65	2py-dibema2-phec-gs
	66	2py-dibema2-phec-ps
	67	2py-dibema2-phec-pms
	68	2py-dibema2-phec-ms
	69	2py-dibema2-phec-mals
10	70	2py-dibema2-phedb-as
	71	2py-dibema2-phepyra-es
	72	2py-dibema2-pyphc-es
	73	2py-dibema2-sulfo-es
	74	2py-dibema2-thiomet-es
15	75	2py-dibema2-thioph-es
	76	2py-dibema2-thioph-gs
	77	2py-dibema2-thioph-ps
	78	2py-dibema2-thioph2-es
	79	2py-dibema2-thiophaz-es
20	80	2py-edia2-8mephec-es
	81	2py-edia2-8mephec-gs
	82	2py-edia2-8mephec-ps
	83	2py-edia2-deophec-es
	84	2py-edia2-deophec-gs
25	85	2py-edia2-deophec-ps
	86	2py-edia2-pheaz-es
	87	2py-edia2-pheaz-ps
	88	2py-edia2-phec-es
	89	2py-edia2-phec-gs
30	90	2py-edia2-phec-ps
	91	2py-edia2-phec-mals
	92	2py-edia2-thioph-es
	93	2py-edia2-thioph-gs
	94	2py-edia2-thioph-ps
35	95	2py-edia2-23dimephec-es
	96	2py-edia2-27dimeophec-es
	97	2py-edia2-2mephec-es
	98	2py-edia2-49dimeophec-es
	99	2py-edia2-5claz-es
40	100	2py-edia2-69dimeophec-es
	101	2py-edia2-69dimephec-es
	102	2py-edia2-78diclphec-es
	103	2py-edia2-78dimeophec-es

	Compound	Structural elements A-E-G-L
	104	2py-edia2-8mepyaz-es
	105	2py-edia2-9clphec-es
5	106	2py-edia2-benz-es
	107	2py-edia2-cl2phec-es
	108	2py-edia2-deothioph-es
	109	2py-edia2-dimepy-es
10	110	2py-edia2-dimepyaz-es
	111	2py-edia2-dimethio-es
	112	2py-edia2-dmaphec-es
	113	2py-edia2-imon-es
	114	2py-edia2-meoaz-es
15	115	2py-edia2-meophe-es
	116	2py-edia2-meophe-nes
	117	2py-edia2-meophe-f2es
	118	2py-edia2-mephe-gs
20	119	2py-edia2-phec-pms
	120	2py-edia2-phec-ms
	121	2py-edia2-phedb-as
	122	2py-edia2-phepyra-es
25	123	2py-edia2-pyphec-es
	124	2py-edia2-sulfo-es
	125	2py-edia2-thiomet-es
	126	2py-edia2-thioph2-es
	127	2py-edia2-thiophaz-es
30	128	2py-edia2-6pyme-pheaz-es
	129	2py-edia2-6pyme-phec-es
	130	2py-edia3-pheaz-es
	131	2py-edia3-phec-es
35	132	2py-edia3-6pyme-pheaz-es
	133	2py-edia3-6pyme-phec-es
	134	2py-edia4-2oxaz-pheaz-es
	135	2py-edia4-2oxaz-phec-es
40	136	2py-edia4-2thiaz-pheaz-es
	137	2py-edia4-2thiaz-phec-es
	138	2py-ediamnebz-pheaz-es
	139	2py-ediamnebz-phec-es
45	140	2py-ediapmebz-pheaz-es
	141	2py-ediapmebz-phec-es
	142	2py-hexa-pheaz-es



	Compound	Structural elements A-E-G-L
	143	2py-hexa-phec-es
	144	2py-inda2-pheaz-es
5	145	2py-inda2-phec-es
	146	2py-me25thima2-pheaz-es
	147	2py-me25thima2-phec-es
	148	2py-me35thima2-pheaz-es
10	149	2py-me35thima2-phec-es
	150	2py-me42thiaz2-pheaz-es
	151	2py-me42thiaz2-phec-es
	152	2py-mea26pyme-pheaz-es
15	153	2py-mea26pyme-phec-es
	154	2py-mea3-pheaz-es
	155	2py-mea3-phec-es
	156	2py-mea36pyme-pheaz-es
	157	2py-mea36pyme-phec-es
20	158	2py-mea42oxaz-pheaz-es
	159	2py-mea42oxaz-phec-es
	160	2py-mea42thiaz-pheaz-es
	161	2py-mea42thiaz-phec-es
25	162	2py-meammbz-pheaz-es
	163	2py-meammbz-phec-es
	164	2py-meapmbz-pheaz-es
	165	2py-meapmbz-phec-es
30	166	2py-mepipe2-pheaz-es
	167	2py-mepipe2-phec-es
	168	2py-mepyma2-pheaz-es
	169	2py-mepyma2-phec-es
	170	2py-penta-8mephec-es
35	171	2py-penta-8mephec-gs
	172	2py-penta-8mephec-ps
	173	2py-penta-deophec-es
	174	2py-penta-deophec-gs
40	175	2py-penta-deophec-ps
	176	2py-penta-pheaz-es
	177	2py-penta-pheaz-ps
	178	2py-penta-phec-es
45	179	2py-penta-phec-gs
	180	2py-penta-phec-ps
	181	2py-penta-thioph-es

	Compound	Structural elements A-E-G-L
	182	2py-penta-thioph-gs
	183	2py-penta-thioph-ps
5	184	2py-pipa2-pheaz-es
	185	2py-pipa2-phec-es
	186	2py-pipeme2-pheaz-es
	187	2py-pipeme2-phec-es
10	188	2py-pyma2-pheaz-es
	189	2py-pyma2-phec-es
	190	3pmhs-am2-pheac-es
	191	3pmhs-dibema2-phec-gs
	192	3pmhs-edia2-phec-es
15	193	4pmhs-am2-pheac-es
	194	4pmhs-dibema2-phec-gs
	195	4pmhs-edia2-phec-es
	196	agua-am2-pheac-es
20	197	agua-dibema2-phec-gs
	198	agua-edia2-phec-es
	199	am2py-am2-8mephec-ps
	200	am2py-am2-8mephec-gs
25	201	am2py-am2-8mephec-es
	202	am2py-am2-pheac-es
	203	am2py-am2-pheaz-ps
	204	am2py-am2-pheaz-gs
	205	am2py-am2-pheaz-es
30	206	am2py-am2-phec-ps
	207	am2py-am2-phec-gs
	208	am2py-am2-phec-es
	209	am2py-am2-phec-es
35	210	am2py-am2-phec-gs
	211	am2py-am2-thioph-ps
	212	am2py-am2-thioph-gs
	213	am2py-am2-thioph-es
40	214	am2py-mea42thiaz-8mephec-ps
	215	am2py-mea42thiaz-8mephec-gs
	216	am2py-mea42thiaz-8mephec-es
	217	am2py-mea42thiaz-pheaz-ps
45	218	am2py-mea42thiaz-pheaz-gs
	219	am2py-mea42thiaz-pheaz-es
	220	am2py-mea42thiaz-phec-ps

Compound	Structural elements A-E-G-L
221	am2py-mea42thiaz-phec-gs
222	am2py-mea42thiaz-phec-es
5 223	am2py-mea42thiaz-thioph-ps
224	am2py-mea42thiaz-thioph-gs
225	am2py-mea42thiaz-thioph-es
226	am4py-am2-pheac-es
10 227	am4py-dibema2-phec-gs
228	am4py-edia2-phec-es
229	amhyd-am2-pheac-es
230	amhyd-am2-phec-es
231	amhyd-am2-phec-gs
15 232	amim-am2-pheac-es
233	amim-am2-phec-es
234	amim-am2-phec-gs
235	amthiz-am2-pheac-es
20 236	amthiz-dibema2-phec-gs
237	amthiz-edia2-phec-es
238	amtriz-am2-pheac-es
239	amtriz-dibema2-phec-gs
25 240	amtriz-edia2-phec-es
241	bgua-am2-pheac-es
242	bgua-dibema2-phec-gs
243	bgua-edia2-phec-es
30 244	bhs-25thima2-phec-gs
245	bhs-35thima2-phec-gs
246	bhs-42thiaz2-phec-gs
247	bhs-aaf-phec-gs
248	bhs-am2-8mephec-es
35 249	bhs-am2-8mephec-gs
250	bhs-am2-8mephec-ps
251	bhs-am2-deophec-es
252	bhs-am2-deophec-gs
40 253	bhs-am2-deophec-ps
254	bhs-am2-pheaz-es
255	bhs-am2-pheaz-ps
256	bhs-am2-phec-es
45 257	bhs-am2-phec-gs
258	bhs-am2-phec-ps
259	bhs-am2-thioph-es

	Compound	Structural elements A-E-G-L
5	260	bhs-am2-thioph-gs
	261	bhs-am2-thioph-ps
	262	bhs-aof-phec-gs
	263	bhs-buta-phec-gs
	264	bhs-chex2-phec-gs
10	265	bhs-dibema2-23dimephec-es
	266	bhs-dibema2-27dimeophec-es
	267	bhs-dibema2-2mephec-es
	268	bhs-dibema2-49dimeophec-es
	269	bhs-dibema2-5claz-es
15	270	bhs-dibema2-69dimeophec-es
	271	bhs-dibema2-69dimephec-es
	272	bhs-dibema2-78diclphec-es
	273	bhs-dibema2-78dimeophec-es
	274	bhs-dibema2-8mephec-es
20	275	bhs-dibema2-8mephec-gs
	276	bhs-dibema2-8mephec-ps
	277	bhs-dibema2-8mepyaz-es
	278	bhs-dibema2-9clphec-es
	279	bhs-dibema2-benz-es
25	280	bhs-dibema2-cl2phec-es
	281	bhs-dibema2-deophec-es
	282	bhs-dibema2-deophec-gs
	283	bhs-dibema2-deophec-ps
	284	bhs-dibema2-deothioph-es
30	285	bhs-dibema2-dimepy-es
	286	bhs-dibema2-dimepyaz-es
	287	bhs-dibema2-dimethio-es
	288	bhs-dibema2-dmaphec-es
	289	bhs-dibema2-imon-es
35	290	bhs-dibema2-meoaz-es
	291	bhs-dibema2-meophe-es
	292	bhs-dibema2-meophe-nes
	293	bhs-dibema2-meophe-f2es
	294	bhs-dibema2-mephe-gs
40	295	bhs-dibema2-pheaz-es
	296	bhs-dibema2-pheaz-ps
	297	bhs-dibema2-phec-es
	298	bhs-dibema2-phec-gs

Compound	Structural elements A-E-G-L
299	bhs-dibema2-phec-ps
300	bhs-dibema2-phec-pms
5 301	bhs-dibema2-phec-ms
302	bhs-dibema2-phec-mals
303	bhs-dibema2-phedb-as
304	bhs-dibema2-phepyra-es
10 305	bhs-dibema2-pyphe-es
306	bhs-dibema2-sulfo-es
307	bhs-dibema2-thiomet-es
308	bhs-dibema2-thioph-es
309	bhs-dibema2-thioph-gs
15 310	bhs-dibema2-thioph-ps
311	bhs-dibema2-thioph2-es
312	bhs-dibema2-thiophaz-es
313	bhs-edia2-8mephec-es
20 314	bhs-edia2-8mephec-gs
315	bhs-edia2-8mephec-ps
316	bhs-edia2-deophec-es
317	bhs-edia2-deophec-gs
25 318	bhs-edia2-deophec-ps
319	bhs-edia2-pheaz-es
320	bhs-edia2-pheaz-ps
321	bhs-edia2-phec-es
30 322	bhs-edia2-phec-gs
323	bhs-edia2-phec-ps
324	bhs-edia2-thioph-es
325	bhs-edia2-thioph-gs
326	bhs-edia2-thioph-ps
35 327	bhs-edia26pyme-phec-gs
328	bhs-edia3-phec-gs
329	bhs-edia36pyme-phec-gs
330	bhs-edia42oxaz-phec-gs
40 331	bhs-edia42thiaz-phec-gs
332	bhs-ediammebz-phec-gs
333	bhs-ediapmebz-phec-gs
334	bhs-hexa-phec-gs
45 335	bhs-inda2-phec-gs
336	bhs-me25thima2-phec-gs
337	bhs-me35thima2-phec-gs

	Compound	Structural elements A-E-G-L
5	338	bhs-me42thiaz2-phec-gs
	339	bhs-mea26pyme-phec-gs
	340	bhs-mea3-phec-gs
	341	bhs-mea36pyme-phec-gs
	342	bhs-mea42oxaz-phec-gs
10	343	bhs-mea42thiaz-phec-gs
	344	bhs-meammebz-phec-gs
	345	bhs-meapmebz-phec-gs
	346	bhs-mepipe2-phec-gs
	347	bhs-mepyma2-phec-gs
15	348	bhs-penta-8mephec-es
	349	bhs-penta-8mephec-gs
	350	bhs-penta-8mephec-ps
	351	bhs-penta-deophec-es
	352	bhs-penta-deophec-gs
20	353	bhs-penta-deophec-ps
	354	bhs-penta-pheaz-es
	355	bhs-penta-pheaz-ps
	356	bhs-penta-phec-es
	357	bhs-penta-phec-gs
25	358	bhs-penta-phec-ps
	359	bhs-penta-thioph-es
	360	bhs-penta-thioph-gs
	361	bhs-penta-thioph-ps
	362	bhs-pipa2-phec-gs
30	363	bhs-pipeme2-phec-gs
	364	bhs-pyma2-phec-gs
	365	bim-25thima2-pheaz-es
	366	bim-35thima2-pheaz-es
	367	bim-42thiaz2-pheaz-es
35	368	bim-aaf-pheaz-es
	369	bim-am2-23dimephec-gs
	370	bim-am2-27dimeophec-gs
	371	bim-am2-2mephec-gs
	372	bim-am2-49dimeophec-gs
40	373	bim-am2-69dimeophec-gs
	374	bim-am2-69dimephec-gs
	375	bim-am2-78diclphec-gs
	376	bim-am2-78dimeophec-gs
	376	bim-am2-78dimeophec-gs

	Compound	Structural elements A-E-G-L
5	377	bim-am2-8mephec-es
	378	bim-am2-8mephec-gs
	379	bim-am2-8mephec-ps
	380	bim-am2-9clphec-gs
	381	bim-am2-cl2phec-gs
10	382	bim-am2-deophec-es
	383	bim-am2-deophec-gs
	384	bim-am2-deophec-ps
	385	bim-am2-deothioph-gs
	386	bim-am2-dimepy-gs
15	387	bim-am2-dimethio-gs
	388	bim-am2-dmaphec-gs
	389	bim-am2-imon-gs
	390	bim-am2-meophe-nes
	391	bim-am2-meophe-f2es
20	392	bim-am2-mephe-gs
	393	bim-am2-pheaz-es
	394	bim-am2-pheaz-ps
	395	bim-am2-phec-es
	396	bim-am2-phec-gs
25	397	bim-am2-phec-ps
	398	bim-am2-phec-pms
	399	bim-am2-phec-ms
	400	bim-am2-phec-mals
	401	bim-am2-phedb-as
30	402	bim-am2-phepyra-gs
	403	bim-am2-pyphc-gs
	404	bim-am2-sulfo-gs
	405	bim-am2-thiomet-gs
	406	bim-am2-thioph-es
35	407	bim-am2-thioph-gs
	408	bim-am2-thioph-ps
	409	bim-am2-thioph2-gs
	410	bim-aof-pheaz-es
	411	bim-buta-pheaz-es
40	412	bim-chex2-pheaz-es
	413	bim-dibema2-8mephec-es
	414	bim-dibema2-8mephec-gs
	415	bim-dibema2-8mephec-ps

	Compound	Structural elements A-E-G-L
5	416	bim-dibema2-deophec-es
	417	bim-dibema2-deophec-gs
	418	bim-dibema2-deophec-ps
	419	bim-dibema2-pheaz-es
	420	bim-dibema2-pheaz-ps
10	421	bim-dibema2-phec-es
	422	bim-dibema2-phec-gs
	423	bim-dibema2-phec-ps
	424	bim-dibema2-thioph-es
	425	bim-dibema2-thioph-gs
15	426	bim-dibema2-thioph-ps
	427	bim-edia2-8mephec-es
	428	bim-edia2-8mephec-gs
	429	bim-edia2-8mephec-ps
	430	bim-edia2-deophec-es
20	431	bim-edia2-deophec-gs
	432	bim-edia2-deophec-ps
	433	bim-edia2-pheaz-es
	434	bim-edia2-pheaz-ps
	435	bim-edia2-phec-es
25	436	bim-edia2-phec-gs
	437	bim-edia2-phec-ps
	438	bim-edia2-thioph-es
	439	bim-edia2-thioph-gs
	440	bim-edia2-thioph-ps
30	441	bim-edia26pyme-pheaz-es
	442	bim-edia3-pheaz-es
	443	bim-edia36pyme-pheaz-es
	444	bim-edia42oxaz-pheaz-es
	445	bim-edia42thiaz-pheaz-es
35	446	bim-ediammebz-pheaz-es
	447	bim-ediapmebz-pheaz-es
	448	bim-hexa-pheaz-es
	449	bim-inda2-pheaz-es
	450	bim-me25thima2-pheaz-es
40	451	bim-me35thima2-pheaz-es
	452	bim-me42thiaz2-pheaz-es
	453	bim-mea26pyme-pheaz-es
	454	bim-mea3-pheaz-es



	Compound	Structural elements A-E-G-L
	455	bim-mea36pyme-pheaz-es
	456	bim-mea42oxaz-pheaz-es
5	457	bim-mea42thiaz-pheaz-es
	458	bim-meammbez-pheaz-es
	459	bim-meapmebz-pheaz-es
	460	bim-mepipe2-pheaz-es
10	461	bim-mepyma2-pheaz-es
	462	bim-penta-8mephec-es
	463	bim-penta-8mephec-gs
	464	bim-penta-8mephec-ps
	465	bim-penta-deophec-es
15	466	bim-penta-deophec-gs
	467	bim-penta-deophec-ps
	468	bim-penta-pheaz-es
	469	bim-penta-pheaz-ps
20	470	bim-penta-phec-es
	471	bim-penta-phec-gs
	472	bim-penta-phec-ps
	473	bim-penta-thioph-es
25	474	bim-penta-thioph-gs
	475	bim-penta-thioph-ps
	476	bim-pipa2-pheaz-es
	477	bim-pipeme2-pheaz-es
30	478	bim-pyma2-pheaz-es
	479	dhim-am2-pheac-es
	480	dhim-dibema2-phec-gs
	481	dhim-edia2-phec-es
	482	dhpyrr-am2-pheac-es
35	483	dhpyrr-dibema2-phec-gs
	484	dhpyrr-edia2-phec-es
	485	dhthi-am2-pheac-es
	486	dhthi-dibema2-phec-gs
40	487	dhthi-edia2-phec-es
	488	dimethpym-am2-pheac-es
	489	dimethpym-dibema2-phec-gs
	490	dimethpym-edia2-phec-es
45	491	gua-am2-pheac-es
	492	gua-dibema2-phec-gs
	493	gua-edia2-phec-es

	Compound	Structural elements A-E-G-L
	494	hs-am2-pheac-es
	495	hs-dibema2-phec-gs
5	496	hs-edia2-phec-es
	497	hts-am2-pheac-es
	498	hts-dibema2-phec-gs
	499	hts-edia2-phec-es
10	500	hyd-am2-pheac-es
	501	hyd-dibema2-phec-gs
	502	hyd-edia2-phec-es
	503	ibhs-am2-pheac-es
	504	ibhs-dibema2-phec-gs
15	505	ibhs-edia2-phec-es
	506	im-am2-pheac-es
	507	im-dibema2-phec-gs
	508	im-edia2-phec-es
20	509	imhs-am2-pheac-es
	510	imhs-dibema2-phec-gs
	511	imhs-edia2-phec-es
	512	impy-am2-8mephec-es
25	513	impy-am2-8mephec-gs
	514	impy-am2-8mephec-ps
	515	impy-am2-deophec-es
	516	impy-am2-deophec-gs
	517	impy-am2-deophec-ps
30	518	impy-am2-pheaz-es
	519	impy-am2-pheaz-ps
	520	impy-am2-phec-es
	521	impy-am2-phec-gs
35	522	impy-am2-phec-ps
	523	impy-am2-thioph-es
	524	impy-am2-thioph-gs
	525	impy-am2-thioph-ps
40	526	impy-dibema2-8mephec-es
	527	impy-dibema2-8mephec-gs
	528	impy-dibema2-8mephec-ps
	529	impy-dibema2-deophec-es
45	530	impy-dibema2-deophec-gs
	531	impy-dibema2-deophec-ps
	532	impy-dibema2-pheaz-es

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	Compound	Structural elements A-E-G-L
	533	impy-dibema2-pheaz-ps
	534	impy-dibema2-phec-es
5	535	impy-dibema2-phec-gs
	536	impy-dibema2-phec-ps
	537	impy-dibema2-thioph-es
	538	impy-dibema2-thioph-gs
10	539	impy-dibema2-thioph-ps
	540	impy-edia2-8mephec-es
	541	impy-edia2-8mephec-gs
	542	impy-edia2-8mephec-ps
15	543	impy-edia2-deophec-es
	544	impy-edia2-deophec-gs
	545	impy-edia2-deophec-ps
	546	impy-edia2-pheaz-es
	547	impy-edia2-pheaz-ps
20	548	impy-edia2-phec-es
	549	impy-edia2-phec-gs
	550	impy-edia2-phec-ps
	551	impy-edia2-thioph-es
25	552	impy-edia2-thioph-gs
	553	impy-edia2-thioph-ps
	554	impy-penta-8mephec-es
	555	impy-penta-8mephec-gs
	556	impy-penta-8mephec-ps
30	557	impy-penta-deophec-es
	558	impy-penta-deophec-gs
	559	impy-penta-deophec-ps
	560	impy-penta-pheaz-es
35	561	impy-penta-pheaz-ps
	562	impy-penta-phec-es
	563	impy-penta-phec-gs
	564	impy-penta-phec-ps
40	565	impy-penta-thioph-es
	566	impy-penta-thioph-gs
	567	impy-penta-thioph-ps
	568	mam2py-am2-pheac-es
45	569	mam2py-dibema2-phec-gs
	570	mam2py-edia2-phec-es
	571	nmhs-am2-pheac-es




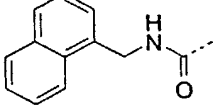
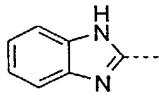
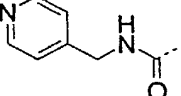
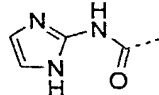

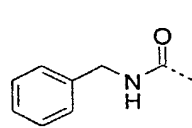
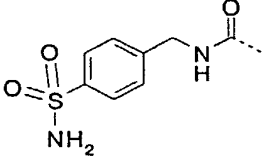
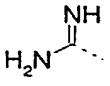
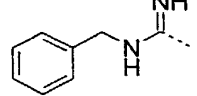
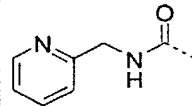

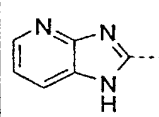
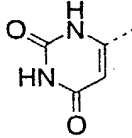
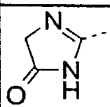
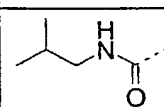
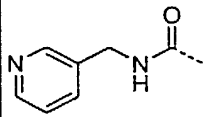
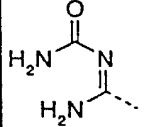
Compound	Structural elements A-E-G-L
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573	nmhs-edia2-phec-es
574	pippy-am2-pheac-es
575	pippy-am2-phec-es
576	pippy-am2-phec-gs
577	piraz-am2-pheac-es
578	piraz-am2-phec-es
579	piraz-am2-phec-gs
580	ppy-am2-pheac-es
581	ppy-dibema2-phec-gs
582	ppy-edia2-phec-es
583	sabhs-am2-pheac-es
584	sabhs-dibema2-phec-gs
585	sabhs-edia2-phec-es
586	thazep-am2-pheac-es
587	thazep-dibema2-phec-gs
588	thazep-edia2-phec-es
589	thiz-am2-pheac-es
590	thiz-dibema2-phec-gs
591	thiz-edia2-phec-es
592	thpy-am2-pheac-es
593	thpy-dibema2-phec-gs
594	thpy-edia2-phec-es
595	thpym-am2-pheac-es
596	thpym-dibema2-phec-gs
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599	ur-dibema2-phec-gs
600	ur-edia2-phec-es

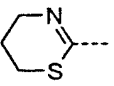
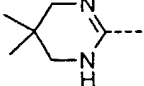
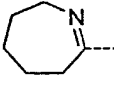
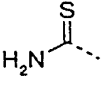
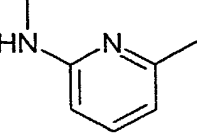
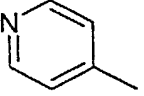
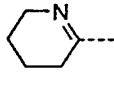
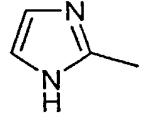
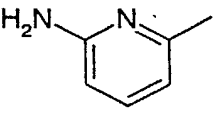
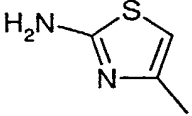
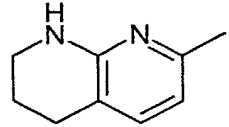
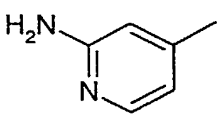
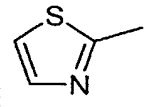
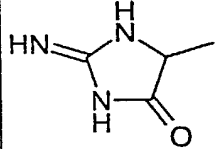
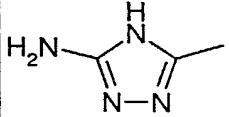
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In the right-hand column of the above table, each line represents a compound. The abbreviations in the right-hand column in each case represent, separated by a hyphen, a structural element A, E, G and L, where the abbreviations have the following meanings:

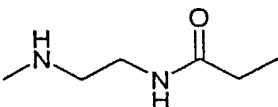
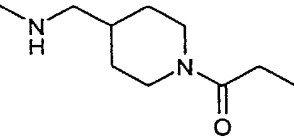
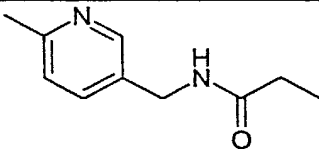
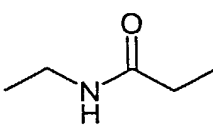
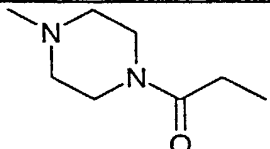
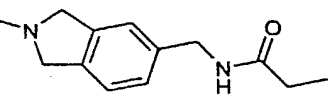
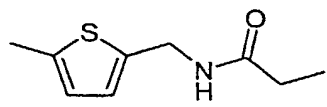
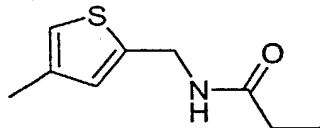
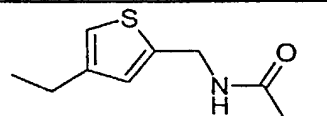
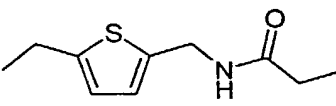
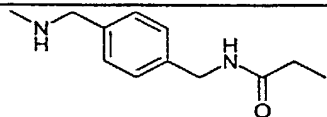
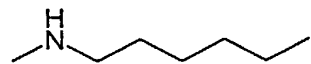
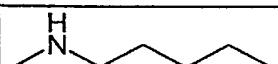

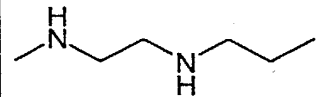
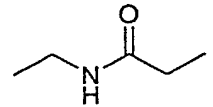
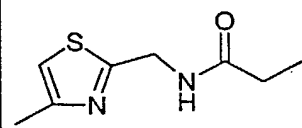
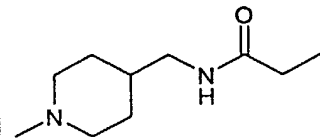
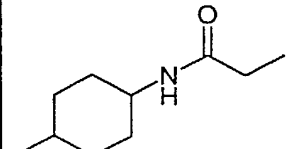
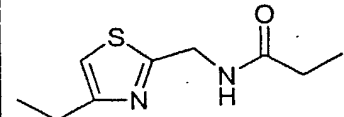
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	A =	Abbreviation	A =	Abbreviation
		2py		thpym
10		dhim		nmhs
15		bim		4pmhs
20		imhs		hs
25		bhs		sabhs
30		gua		bgua
35		2pmhs		dhprr
		impy		ur
40		hyd		ibhs
45		3pmhs		agua

	A =	Abbreviation	A =	Abbreviation
5		dhthi		dimethpym
		thazep		hts
10		mam2py		ppy
15		thpy		im
20		am2py		amthiz
25		pippy		am4py
30		thiz		amhyd
35		amtriz		

40

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	E =	Abbreviation	E =	Abbreviation
5		edia2		mepipe2
10		pyma2		am2
15		pipa2		inda2
20		25thima2		35thima2
25		me35thima2		me25thima2
30		dibema2		penta
35		buta		hexa
		aaf		mea2
40		42thiaz2		pipeme2
45		chex2		me42thiaz2

57

	E =	Abbreviation	E =	Abbreviation
5		mepyma2		mea3
10		edia42-thiaz		mea42-thiaz
15		edia42-oxaz		mea42oxaz
20		ediapmebz		ediammebz
25		edia26-pyme		edia36-pyme
30		mea26pyme		mea36pyme

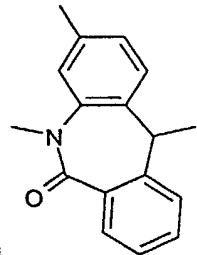
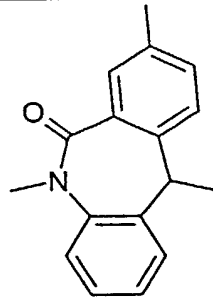
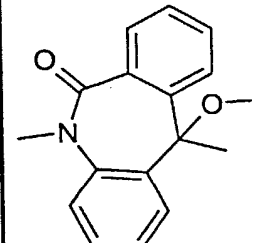
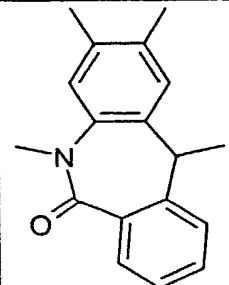
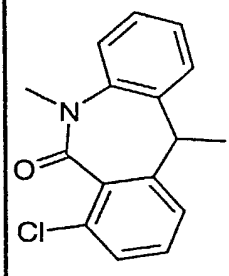
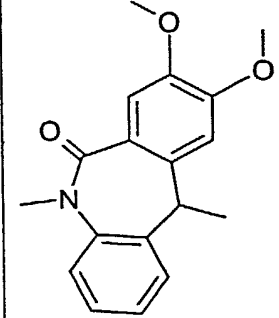
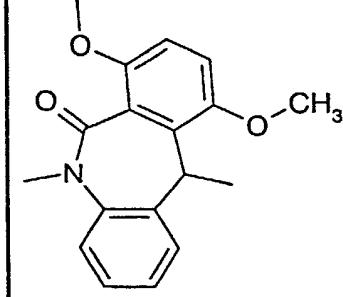
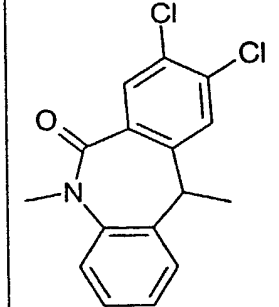
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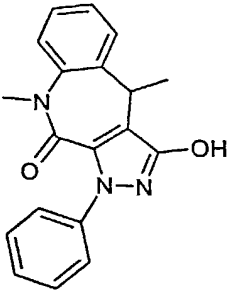
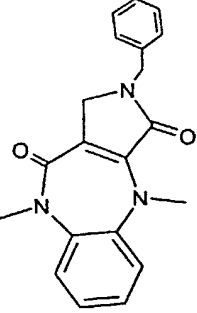
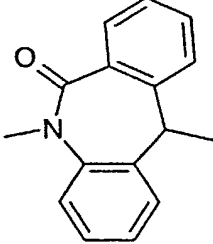
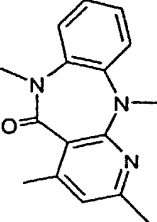
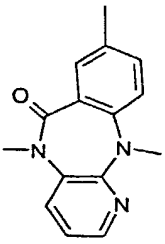
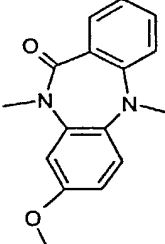
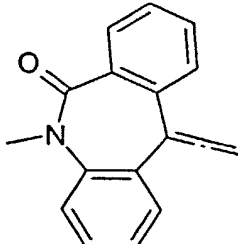
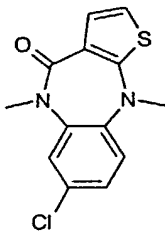
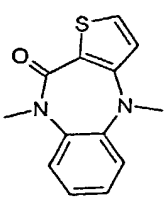
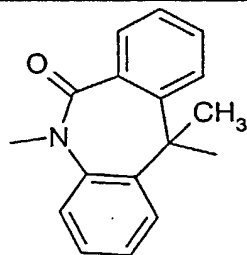
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	G =	Abbreviation	G =	Abbreviation
5		2mephec		8mephec
10		meophe		23dimephec
15		9clphec		78dimeophec
20		69dimeophec		78diclphec
25				
30				
35				
40				

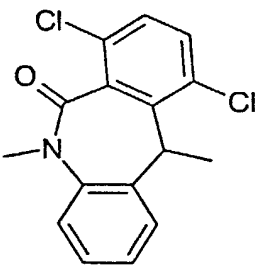
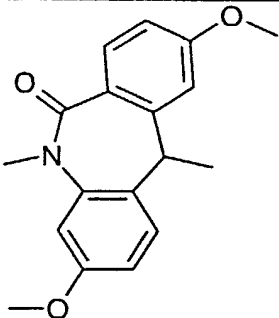
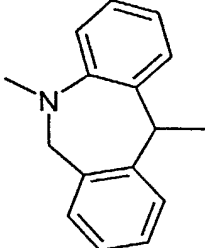
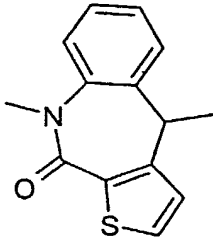
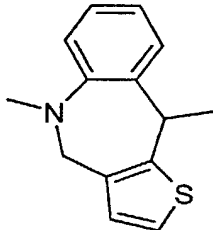
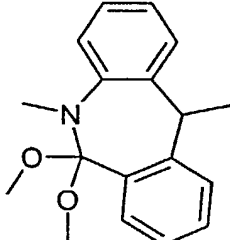
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	G =	Abbreviation	G =	Abbreviation
5		69dimephec		49dimeophec
10				
15		imon		dimepy
20				
25		dimethio		sulfo
30		pyphc		thioph
35				
40		pheaz		thiomet

60

G =	Abbreviation	G =	Abbreviation
5  10	phepyra	 benz	
15  20	phec	 dimepyaz	
25  30	8mepyaz	 meoaz	
35  40	phedb	 5claz	
45 	thiophaz	 mephe	

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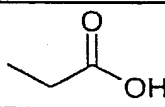
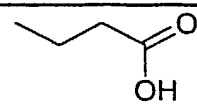
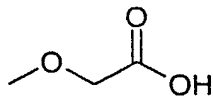
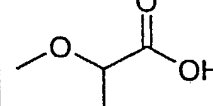
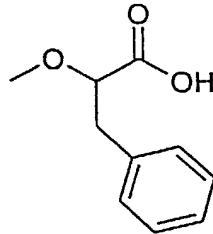
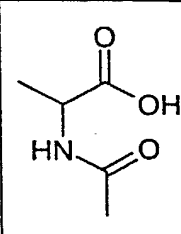
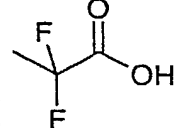
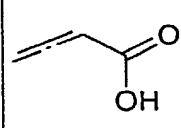
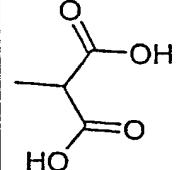
	G =	Abbrev- iation	G =	Abbrev- iation
5		cl2phec		27dimeophec
15		deophec		thioph2
25		deothioph		dmaphec

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45

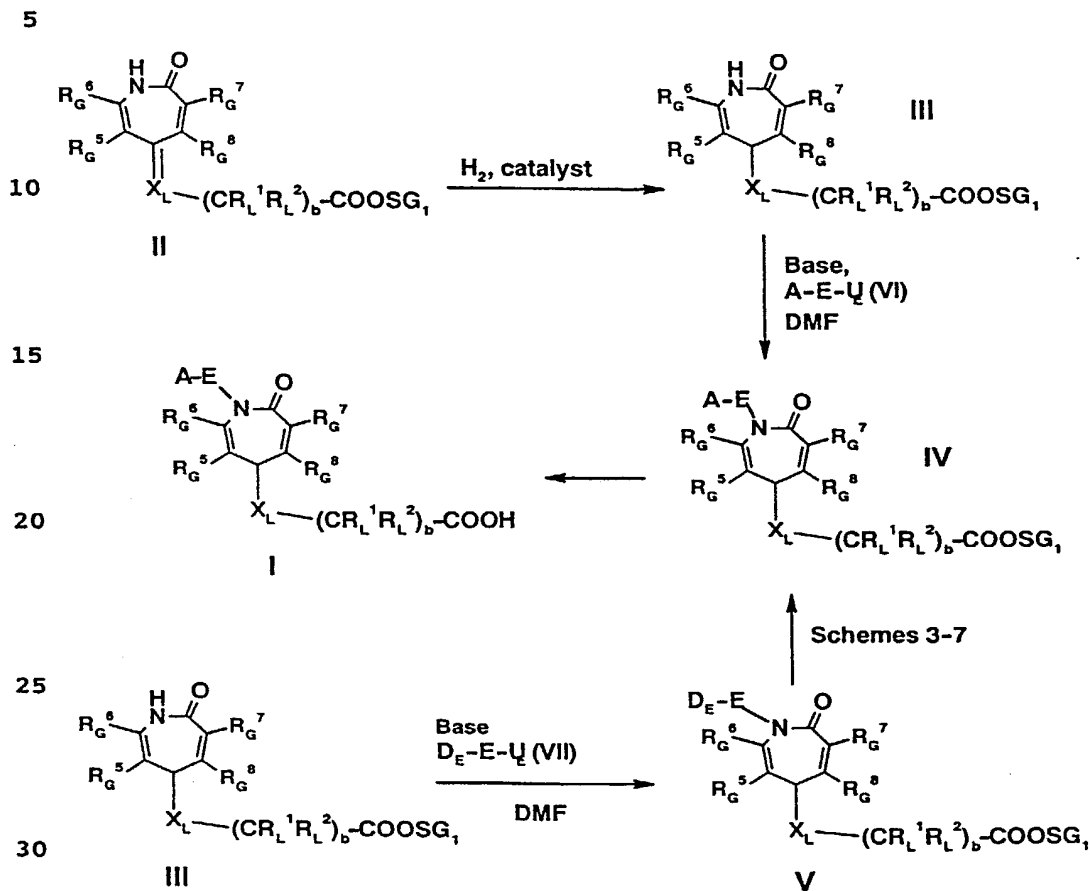
	L =	Abbreviation	L =	Abbreviation
5		es		ps
		gs		ms
10		pms		nes
15				
20		f2es		as
25		mals		

Compounds of the general formula I and the starting materials  
 30 used to prepare them can generally be prepared by methods of  
 organic chemistry known to the skilled worker as described in  
 standard works such as, for example, Houben-Weyl, "Methoden der  
 Organischen Chemie", Thieme-Verlag, Stuttgart, or March "Advanced  
 Organic Chemistry", 4th Edition, Wiley & Sons. Further  
 35 preparation methods are also described in R. Larock,  
 "Comprehensive Organic Transformations", Weinheim 1989, in  
 particular the preparation of alkenes, alkynes, halides, amines,  
 ethers, alcohols, phenols, aldehydes, ketones, nitriles,  
 carboxylic acids, esters, amides and acid chlorides.

40 The general synthesis of compounds of the formula I where A-E-  
 represents B is described in schemes 1-7. Unless otherwise  
 indicated, all the starting materials and reagents can be bought  
 or can be prepared by conventional methods from precursors which  
 45 can be bought.

Scheme 1 describes the synthesis of compounds of the formula I in general.

Scheme 1



Building blocks of type II (for X<sub>L</sub> equal to CH) are known and can be prepared by known methods starting from appropriately substituted or fused 1H-azepine-2,5-diones as described by way of example e.g. in J. Med. Chem. 1986, 29, 1877-1888 or DE 1568217. 1H-Azepine-2,5-diones used to prepare compounds of type I can either be bought or be prepared as described in the following publications:

40

5H-Dibenzo[b,e]azepine-6,11-dione and substituted variants according to J. Med. Chem. 1965, 8, 74 or Gazz. Chim. Ital. 1953, 83, 533 and 1954, 84, 1135;

5H-pyrido[3,2-c][1]benzazepine-5,11(6H)-dione according to 45 Liebigs Ann. Chem. 1989, 469-476;

4H-thieno[3,2-c][1]benzazepine-4,10(5H)-dione according to Eur. J. Med. Chem. Ther. 1981, 16, 391-398.

The conversion to III is carried out by hydrogenating the double bond under standard conditions. It is also possible for this to make use of variants which are known per se but which are not mentioned here. The hydrogenation is preferably carried out in the presence of a noble metal catalyst such as, for example, Pd on active carbon, Pt, PtO<sub>2</sub>, Rh on Al<sub>2</sub>O<sub>3</sub> in an inert solvent at a temperature of 0-150°C under a pressure of 1-200 bar; addition of an acid such as, for example, acetic acid or hydrochloric acid may be advantageous. Hydrogenation in the presence of 5-10% Pd on active carbon is particularly preferred.

Solvents which can be used are all conventional inert solvents such as, for example, hydrocarbons such as hexane, heptane, petroleum ether, toluene, benzene or xylene; chlorinated hydrocarbons such as trichloroethylene, 1,2-dichloroethane, carbon tetrachloride, chloroform, dichloromethane; alcohols such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers such as diethyl ether, methyl tert-butyl ether, diisopropyl ether, tetrahydrofuran, dioxane; glycol ethers such as ethylene glycol monomethyl ether or monoethyl ether, ethylene glycol dimethyl ether; ketones such as acetone, butanone; amides such as dimethylformamide (DMF), dimethylacetamide or acetamide; sulfoxides such as dimethyl sulfoxide, sulfolane; pyridine, N-methylpyrrolidone, 1,3-dimethyltetrahydro-2(1H)-pyrimidinone (DMPU), 1,3-dimethyl-2-imidazolidinone, water or mixtures of said solvents.

Compounds of type IV are prepared by reaction with compounds of the general formula A-E-U<sub>E</sub> (VI), where the U<sub>E</sub> radical is a conventional leaving group, for example halogen such as chlorine, bromine, iodine or an optionally halogen-, alkyl- or haloalkyl-substituted aryl- or alkylsulfonyloxy radical such as, for example, toluenesulfonyloxy, trifluoromethanesulfonyloxy and methylsulfonyloxy or another equivalent leaving group.

The reaction preferably takes place in an inert solvent with the addition of a suitable base, i.e. a base which deprotonates the intermediate III, at a temperature in the range from -40°C to the boiling point of the appropriate solvent.

The base which can be used is an alkali metal or alkaline earth metal hydride such as sodium hydride, potassium hydride or calcium hydride, a carbonate such as alkali metal carbonate, for example sodium or potassium carbonate, an alkali metal or

alkaline earth metal hydroxide such as sodium or potassium hydroxide, an alcoholate such as, for example, sodium methanolate, potassium tert-butanolate, an organometallic compound such as butyllithium or alkali metal amides such as lithium diisopropylamide, lithium, sodium or potassium bis(trimethylsilyl)amide.

Elimination of the protective group SG1 under standard conditions (see below) results in the compounds of the general formula I.

10 Where SG1 is equal to C<sub>1</sub>-C<sub>4</sub>-alkyl or benzyl, the compounds of the general formula IV correspond directly to the compounds of type I.

As an alternative to this synthetic strategy, compounds of type I  
15 can also be prepared via V as intermediate, in which case the reaction conditions used are those known to the skilled worker and described in standard works. Compound V is prepared by reacting compounds of type III with compounds of the general formula D<sub>E</sub>-E-U<sub>E</sub> (VII) under the reaction conditions already  
20 described for preparing IV. U<sub>E</sub> is a suitable leaving group as described above, and D<sub>E</sub> is CN or a protected amino or acid function of the general formula NSG<sub>3</sub> or COOSG<sub>2</sub>. The fragments D<sub>E</sub>-E and A-E are synthesized - depending on the actual structure of E - by eliminating the protective groups and coupling on the  
25 remaining fragments by standard methods, for example amide coupling. The introduction of A then takes place in analogy to the reactions described in schemes 3-7.

Compounds of type I in which X<sub>G</sub> is N can be prepared as shown in  
30 scheme 2.

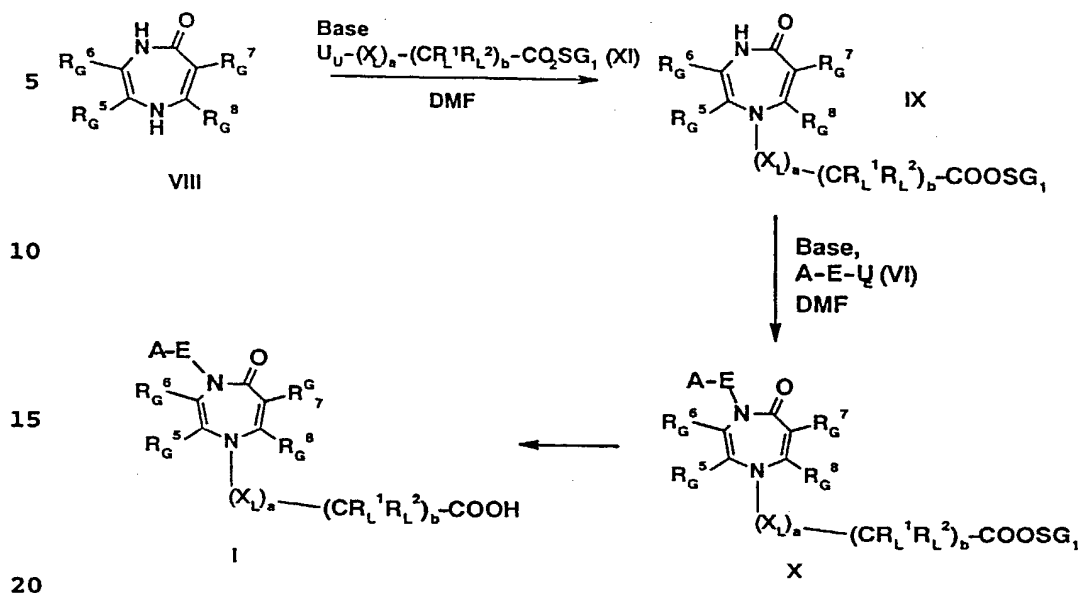
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Scheme 2



The synthesis starts from compounds of type VIII which are either known or accessible to the skilled worker by known methods as described, for example, in Pharmazie 45 (8), 1990, 555-559.

- 25 Alkylation with a compound of the general formula XI ( $U_U$  = conventional leaving group as described above for  $U_E$ ) under the reaction conditions described for preparing substances of type IV results in IX. The subsequent reactions to I via X take place in analogy to Scheme 1.

30

The coupling of the individual fragments and the elimination of the protective groups can take place by known processes (see Larock, "Comprehensive Organic Transformations"; protective groups: Greene and Wuts, T., "Protective Groups in Organic

- 35 Synthesis", New York 1991), and in the case of amide linkages also analogous to the methods of peptide synthesis as described in standard works, for example in Bodanszky "The Practice of Peptide Synthesis", 2nd Edition, Springer-Verlag 1994, and Bodanszky "Principles of Peptide Synthesis", Springer-Verlag

- 40 1984. A general review of the conventional methods for peptide synthesis and a listing of suitable reagents can moreover be found in NOVABIOCHEM 1999 "Catalog and Peptide Synthesis Handbook".

- 45 Said amide couplings can be carried out with the aid of conventional coupling reagents using suitably protected amino and carboxylic acid derivatives. Another method comprises the use of

preactivated carboxylic acid derivatives, preferably of carbonyl halides, symmetrical or mixed anhydrides or so-called active esters, which are normally used to acylate amines. These activated carboxylic acid derivatives can also be prepared in situ. The couplings can usually be carried out in inert solvents in the presence of an acid-binding agent, preferably an organic base such as, for example, triethylamine, pyridine, diisopropylethylamine, N-methylmorpholine, quinoline; it may also be beneficial to add an alkali metal or alkaline earth metal hydroxide, carbonate or bicarbonate or another weak acid salt of the alkali metals or alkaline earth metals, preferably of potassium, sodium, calcium or cesium.

The reaction time is between minutes and 14 days, and the reaction temperature is between -40°C and 140°C, preferably between -20°C and 100°C, depending on the conditions used.

Examples of suitable inert solvents are hydrocarbons such as hexane, heptane, petroleum ether, toluene, benzene or xylene; chlorinated hydrocarbons such as trichloroethylene, 1,2-dichloroethane, tetrachloromethane, chloroform, dichloromethane; alcohols such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers such as diethyl ether, methyl tert-butyl ether, diisopropyl ether, tetrahydrofuran, dioxane; glycol ethers such as ethylene glycol monomethyl ether or monoethyl ether, ethylene glycol dimethyl ether; ketones such as acetone, butanone; amides such as dimethylformamide (DMF), dimethylacetamide or acetamide; nitriles such as acetonitrile; sulfoxides such as dimethyl sulfoxide, sulfolane; N-methylpyrrolidone, 1,3-dimethyltetrahydro-2(1H)-pyrimidinone (DMPU), 1,3-dimethyl-2-imidazolidinone, nitro compounds such as nitromethane or nitrobenzene; esters such as ethyl acetate; water; or mixtures of said solvents.

The protective groups SG which can be used are all conventional protective groups known to the skilled worker from peptide synthesis, as are also described in the abovementioned standard works.

Elimination of the protective groups in the compounds of the formula IV, V, VI and VII likewise takes place under conditions known to the skilled worker and described, for example, by Greene and Wuts in "Protective Groups in Organic Synthesis", 2nd Edition, Wiley & Sons, 1991.

Protective groups such as SG<sub>3</sub> are so-called N-terminal amino protective groups; those preferred for this are Boc, Fmoc, benzyloxycarbonyl (Z), acetyl or Mtr.

- 5 SG<sub>1</sub> and SG<sub>2</sub> are so-called C-terminal hydroxyl protective groups, and these are preferably C<sub>1</sub>-C<sub>4</sub>-alkyl such as, for example, methyl, ethyl, tert-butyl or else benzyl or trityl, or else polymer-bound protective groups in the form of the commercially available polystyrene resins such as, for example, 2-chlorotrityl chloride-  
10 resin or Wang resin (supplied by Bachem, Novabiochem).

- Acid-labile protective groups (for example Boc, tert-butyl, Mtr, trityl) can be eliminated - depending on the protective group used - with organic acids such as trifluoroacetic acid (TFA),  
15 trichloroacetic acid, perchloric acid, trifluoroethanol; but also inorganic acids such as hydrochloric acid or sulfuric acid, sulfonic acids such as benzene- or p-toluenesulfonic acid, with the acids generally being employed in excess. In the case of trityl it may be advantageous to add thiols such as, for example,  
20 thioanisole or thiophenol. The presence of an additional inert solvent is possible but not always necessary. Suitable and preferred inert solvents are organic solvents, for example carboxylic acids such as acetic acid; ethers such as THF or dioxane; amides such as DMF or dimethylacetamide; halogenated  
25 hydrocarbons such as dichloromethane; alcohols such as methanol, isopropanol; or water. Mixtures of said solvents are also suitable.

- The temperature for these reactions is between 10°C and 50°C,  
30 preferably in the range between 0°C and 30°C.

- Base-labile protective groups such as fmoc are cleaved by treatment with organic amines such as dimethylamine, diethylamine, morpholine, piperidine as 5-50% solutions in CH<sub>2</sub>Cl<sub>2</sub>,  
35 or DMF. The temperature for these reactions is between 10°C and 50°C, preferably in the range between 0°C and 30°C.

- Acid-protective groups such as methyl or ethyl are preferably cleaved by basic hydrolysis in an inert solvent. The bases  
40 preferably used are alkali metal or alkaline earth metal hydroxides, preferably NaOH, KOH or LiOH;

- the solvents used are all conventional inert solvents such as, for example, hydrocarbons such as hexane, heptane, petroleum  
45 ether, toluene, benzene or xylene; chlorinated hydrocarbons such as trichloroethylene, 1,2-dichloroethane, tetrachloromethane, chloroform, dichloromethane; alcohols such as methanol, ethanol,

- isopropanol, n-propanol, n-butanol or tert-butanol; ethers such as diethyl ether, methyl tert-butyl ether, diisopropyl ether, tetrahydrofuran, dioxane; glycol ethers such as ethylene glycol monomethyl ether or monoethyl ether, ethylene glycol dimethyl ether; ketones such as acetone, butanone; amides such as dimethylformamide (DMF), dimethylacetamide or acetamide; nitriles such as acetonitrile; sulfoxides such as dimethyl sulfoxide, sulfolane; N-methylpyrrolidone, 1,3-dimethyltetrahydro-2(1H)-pyrimidinone (DMPU), 1,3-dimethyl-2-imidazolidinone; nitro compounds such as nitromethane or nitrobenzene; water or mixtures of said solvents. Addition of a phase-transfer catalyst may be advantageous, depending on the solvent or mixture thereof used. The temperature for these reactions is generally between -10°C and 100°C.
- 15 Protective groups which can be eliminated by hydrogenolysis, such as benzyloxycarbonyl (Z) or benzyl can be eliminated, for example, by hydrogenolysis in the presence of a catalyst (for example a noble metal catalyst on active carbon as support).
- 20 Suitable solvents are those indicated above, in particular alcohols such as methanol, ethanol; amides such as DMF or dimethylacetamide; esters such as ethyl acetate. The hydrogenolysis is usually carried out under a pressure of from 1 to 200 bar and at temperatures between 0°C and 100°C; addition of an acid such as, for example, acetic acid or hydrochloric acid may be advantageous. 5 to 10% Pd on active carbon is preferably used as catalyst.

- The synthesis of building blocks of type E generally takes place by methods known to the skilled worker; the building blocks used can either be bought or be obtained by methods known from the literature. The synthesis of some of these building blocks is described by way of example in the experimental section.
- 35 In the case where the fragments  $Q_E$  and  $X_E$  present in the compounds of type V and VI are a hetaryl radical, the radical E can be synthesized via compounds of type VI-VII starting from aminohetaryl carboxylic acids, aminohetaryl carboxylic esters or nitriles by described methods known to the skilled worker. A large number of preparation methods are described in detail in Houben-Weyls "Methoden der organischen Chemie" (Vol. E6: Furans, thiophenes, pyrroles, indoles, benzothiophenes, -furans, -pyrroles; Vol. E7: Quinolines, pyridines, Vol. E8: Isoxazoles, oxazoles, thiazoles, pyrazoles, imidazoles and benzo-fused representatives thereof, and oxadiazoles, thiadiazoles and triazoles; Vol. E9: Pyridazines, pyrimidines, triazines, azepines and the benzo-fused representatives thereof, and purines). The

linkage of these fragments to E can also take place via the amino or acid function, depending on the structure of E, by methods known to the skilled worker.

5 Appropriate hetaryl derivatives can either be bought or be prepared in analogy to the following publications:

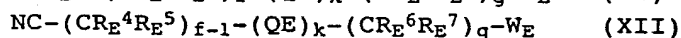
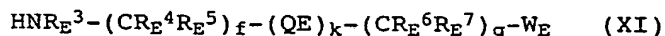
- 5-(Aminomethyl)-2-pyridinecarbonitrile according to WO 95/25426,  
5-(Aminomethyl)-3-thiophenecarbonitrile according to WO 98/06741,  
10 5-(Aminomethyl)-2-thiophenecarbonitrile in WO 95/23609,  
2-(Aminomethyl)-1,3-thiazole-4-carbonitrile in analogy to WO 98/06741,  
3-Oxo-5-isoindolinecarboxylic acid according to WO 97/37655,  
3-Amino-2-pyrrolidone according to WO 98/44797,  
15 Spirocycles such as  
8-(aminomethyl)-2-oxa-3-azaspiro[4.5]dec-3-en-4-yl acetate and  
7-(aminomethyl)-2-oxa-3-azaspiro[4.4]non-3-en-4-yl acetate  
according to WO 97/33887,  
[5-(2-Aminoalkyl)-4,5-dihydro-3-isoxazolyl]carboxylic acid and  
20 acetate, [3-(2-aminoalkyl)-4,5-dihydro-5-isoxazolyl]carboxylic  
acid and acetate according to WO 96/37492,  
1-(3-Aminoalkyl)-1H-indazole-5-carboxylic acid according to WO 97/23480;  
Ethyl 2-amino-1,3-thiazole-5-carboxylate in Kushner et al., J.  
25 Org. Chem. 1948, 13, 834ff;  
Methyl 2-amino-4-pyridinecarboxylate in Podany et al., J. Org.  
Chem. 1986, 51, 2988-2994;  
Methyl 5-amino-3-pyridinecarboxylate in Hawkins et al., J. Org.  
Chem. 1949, 14, 328-332;  
30 Methyl 4-amino-2-pyrimidinecarboxylate in DE 2848912,  
Methyl 6-amino-4-pyrimidinecarboxylate in Zh. Org. Khim. 1981,  
17, 312-317;  
Ethyl 5-amino-1,3-thiazole-2-carboxylate in Adams et al., J.  
Chem. Soc. 1956, 1870-1873;  
35 Methyl 4-(aminomethyl)-2-thiophenecarboxylate in Peschke et al.,  
Bioorg. Med. Chem. Lett. 1997, 7, 1969-1972;  
2-Amino-1,3-oxazole-4-carboxylic acid in Foulis et al., J. Med.  
Chem. 1971, 14, 1075-1077;  
Methyl 4-aminopyridine-2-carboxylate in Mostier et al., J. Org.  
40 Chem. 1955, 20, 283-285;  
Methyl 2-aminopyrimidine-3-carboxylate in Liebigs Ann. Chem.  
1965, 209-211;  
5-Amino-1,3,4-thiadiazole-5-carboxylic acid in Liebigs Ann. Chem.  
1963, 3;  
45 5-Amino-1,3,4-triazole-5-carboxylic acid in US 3023210;  
4-Aminopyrrole-2-carboxylic acid in J. Med. Chem. 1983, 26, 1042;

1-Methyl-3-aminopyrazole-5-carboxylic acid in Acta Chem. Scand. 1990, 44, 74;

1-Methyl-5-aminopyrazole-3-carboxylic acid in Lee et al., J. Org. Chem. 1989, 54, 428.

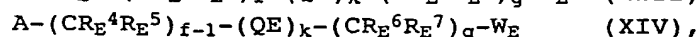
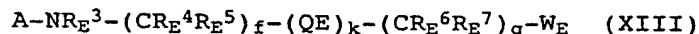
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Conversion of compounds of the general formula XI and XII



10

into compounds of the general formula:



15

where  $\text{W}_E$  is  $\text{COOSG}_2$  or  $\text{NSG}_3$ ,

can take place by methods known to the skilled worker and described, for example, in WO 97/08145. These building blocks can then be converted either directly - in the case of the corresponding free amines and carboxylic acids - or after elimination of the protective groups - into compounds of the general formula I (scheme 1).

20

However, it is also possible in principle for A to be introduced, as described in scheme 1, into compounds of type V, in which case the stated reaction conditions can be used, just as can variants not described here.

25

In schemes 3-7, a number of methods for introducing A are described by way of example, using in each case reaction conditions known and suitable for the particular reactions. It is moreover possible to make use of variants which are known per se but which are not mentioned here.

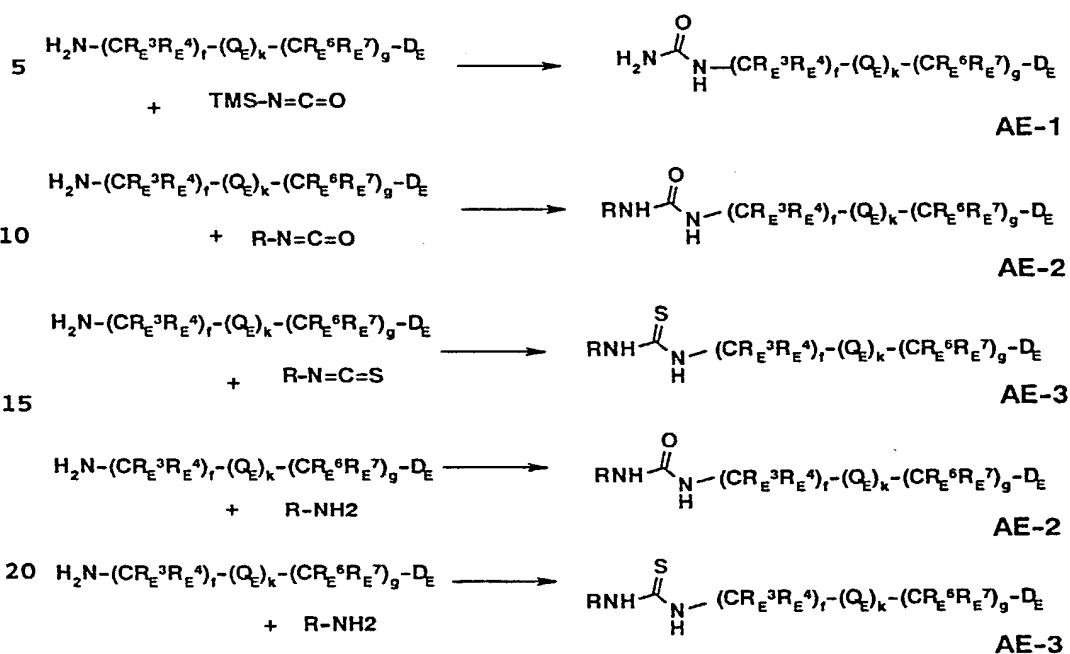
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Scheme 3



25 Ureas or thioureas (AE-1 to AE-3) can be prepared by conventional methods of organic chemistry, for example by reacting an isocyanate or an isothiocyanate with an amine, where appropriate in an inert solvent with heating (Houben-Weyl, Vol. VIII, 157 et seq.) (scheme 3).

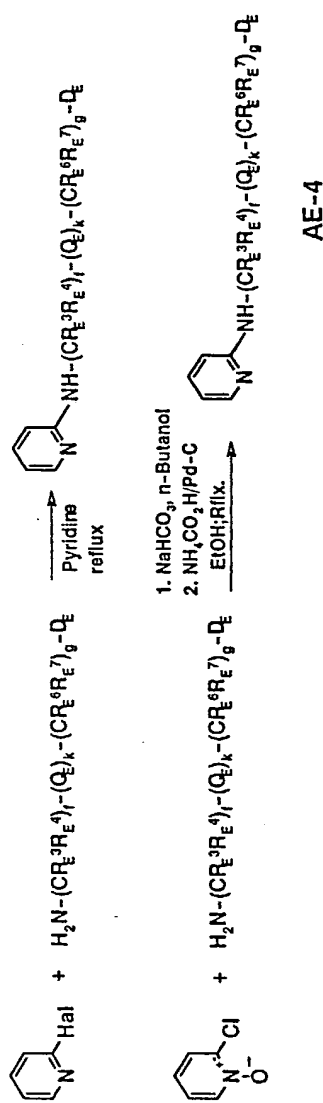
30 Scheme 4 shows by way of example the preparation of compounds of type AE-4 as described, for example, by Blakemoore et al. in Eur. J. Med. Chem. 1987 (22) 2, 91-100, or by Misra et al. in Bioorg. Med. Chem. Lett. 1994, 4 (18), 2165-2170.

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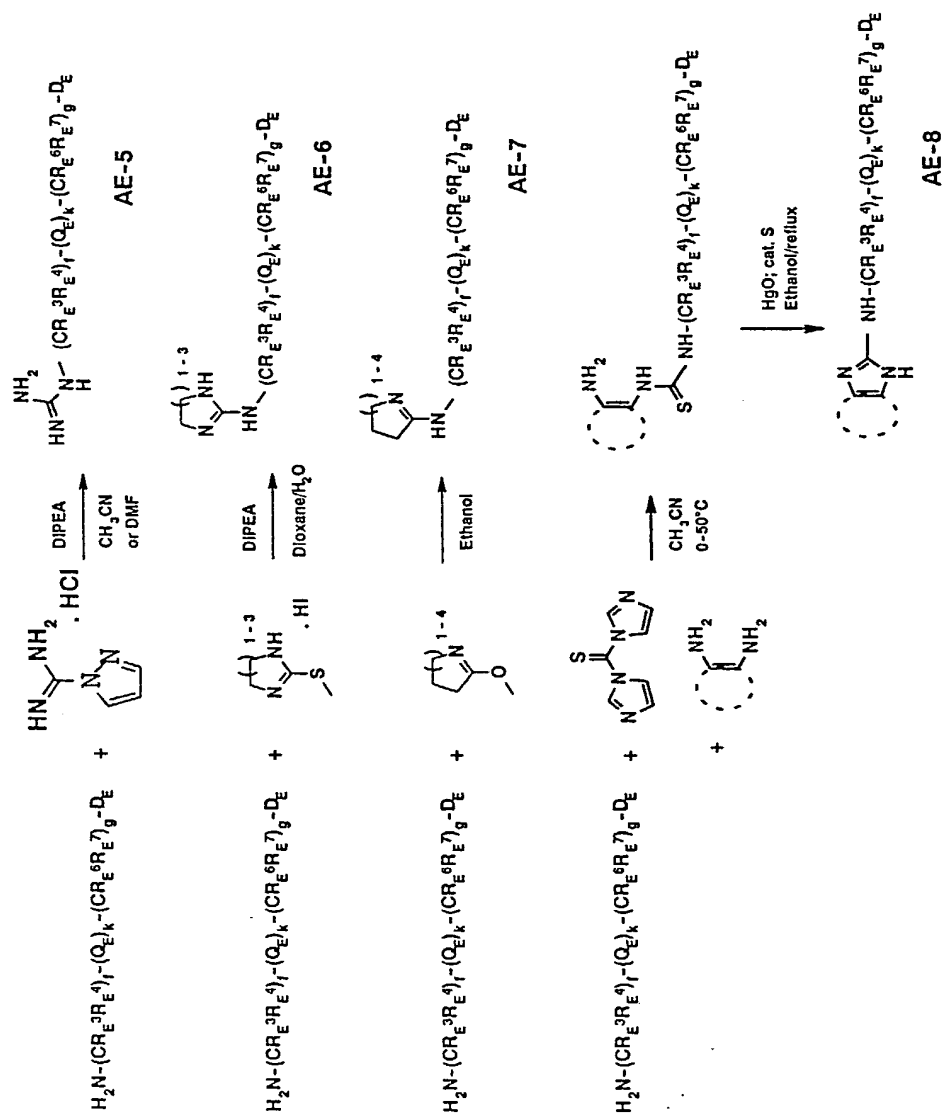
Scheme 4

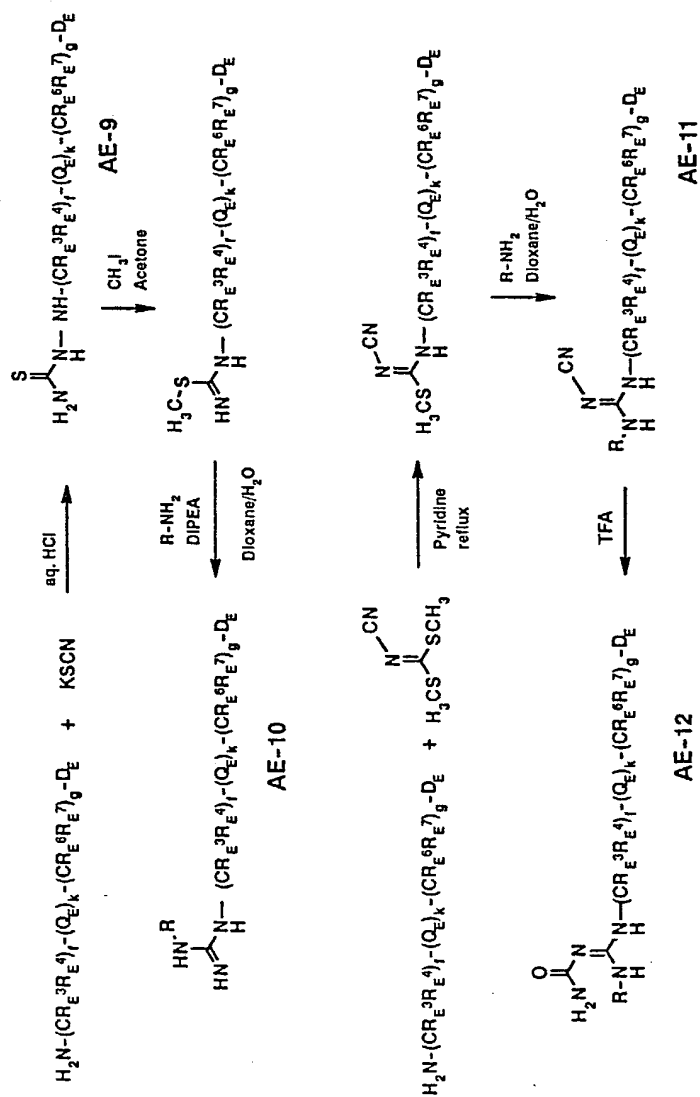


Unsubstituted or cyclic guanidine derivatives of the general formula AE-5 and AE-6 can be prepared using reagents which can be bought or obtained simply, as described, for example, in Synlett 1990, 745, J. Org. Chem. 1992, 57, 2497, Bioorg. Med. Chem. 1996, 6, 1185-1208; Bioorg. Med. Chem. 1998, 1185, or Synth. Comm. 1998, 28, 741-746.



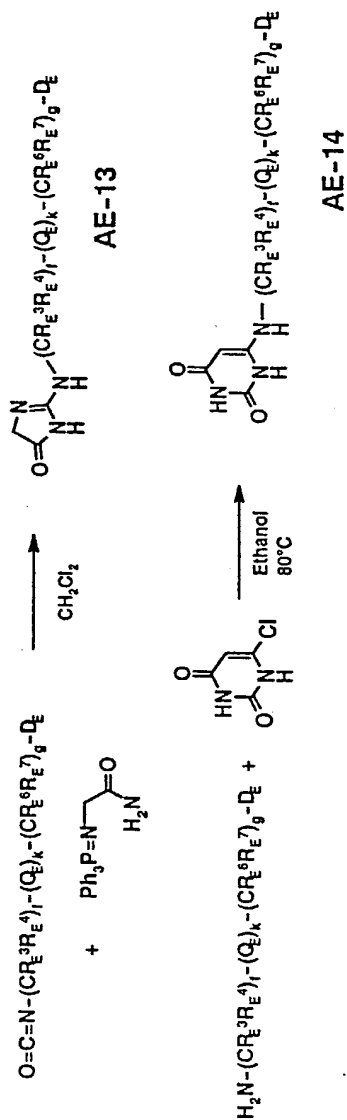
Scheme 5





Preparation of compounds of the general formula AE-7 can take place in analogy to US 3,202,660, and compounds of the formula AE-9, AE-10, AE-11 and AE-12 in analogy to WO 97/08145. Compounds of the formula AE-8 can be prepared, as shown in Scheme 6, for example by the method described by Perkins et al., Tetrahedron Lett. 1999, 40, 1103-1106. Scheme 6 summarizes the synthesis of said compounds:

Scheme 6



Compounds of the general formula AE-13 can be prepared in analogy to Froeyen et al., Phosphorus Sulfur Silicon Relat. Elem. 1991, 63, 283-293, AE-14 in analogy to Yoneda et al., Heterocycles 1998, 15 N°-1, Spec. Issue, 341-344 (scheme 7). The preparation of corresponding compounds can also take place in analogy to WO 97/36859.

Compounds of the general formula AE-15 can be prepared as in 10 Synthesis 1981, 963-965 or Synth. Comm. 1997, 27 (15), 2701-2707, AE-16 in analogy to J. Org. Chem. 1991, 56 (6), 2260-2262 (scheme 7).

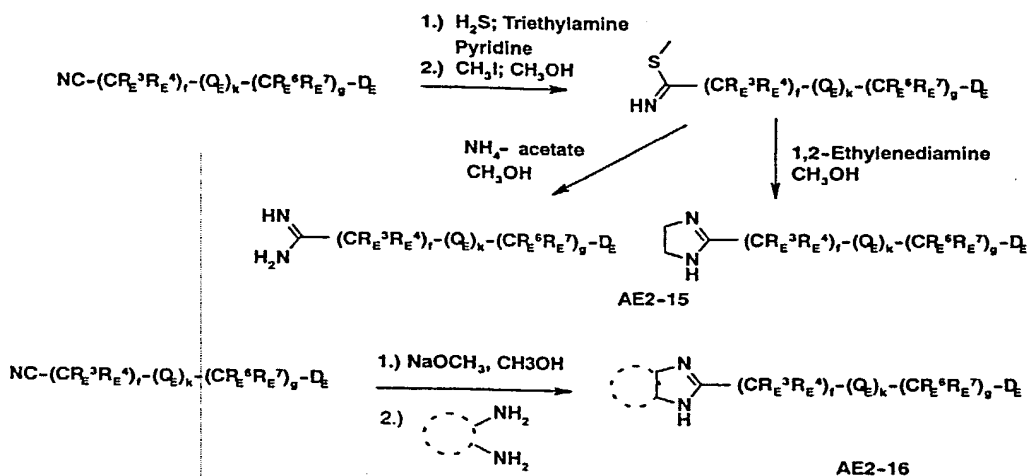
Scheme 7

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30



The invention further relates to the use of the structural element of the formula  $\text{I}_{\text{GL}}$

35

-G-L

 $\text{I}_{\text{GL}}$ 

for preparing compounds which bind to integrin receptors.

40 The invention further relates to drugs comprising the structural element of the formula  $\text{I}_{\text{GL}}$ .

The invention further relates to pharmaceutical preparations for oral and parenteral use containing at least one compound of the 45 formula I in addition to conventional pharmaceutical excipients.

The compounds according to the invention can be administered orally or parenterally (subcutaneously, intravenously, intramuscularly, intraperitoneally) in a conventional way. Administration can also take place with vapors or sprays through  
5 the nasopharyngeal space.

The dosage depends on the age, condition and weight of the patient and on the mode of administration. As a rule, the daily dose of active ingredient is between about 0.5 and 50 mg/kg of  
10 body weight on oral administration and between about 0.1 and 10 mg/kg of body weight on parenteral administration.

The novel compounds can be used in conventional solid or liquid pharmaceutical forms, for example as uncoated or (film-)coated  
15 tablets, capsules, powders, granules, suppositories, solutions, ointments, creams or sprays. These are produced in a conventional way. The active ingredients can for this purpose be processed with conventional pharmaceutical aids such as tablet binders, bulking agents, preservatives, tablet disintegrants, flow  
20 regulators, plasticizers, wetting agents, dispersants, emulsifiers, solvents, release-slowing agents, antioxidants and/or propellant gases (cf. H. Sucker et al.: Pharmazeutische Technologie, Thieme-Verlag, Stuttgart, 1991). The administration forms obtained in this way normally contain from 0.1 to 90% by  
25 weight of active ingredient.

The invention further relates to the use of the compounds of the formula I for producing drugs for the treatment of diseases. The compounds of the formula I can be used for treating human and  
30 animal diseases. The compounds of the formula I bind to integrin receptors. They are therefore suitable preferably as integrin receptor ligands and for producing drugs for treating diseases in which an integrin receptor is involved.

35 They can preferably be used to produce drugs for treating diseases in which, for example, there is excessive interaction between integrins and their natural ligands.

The compounds of the formula I preferentially bind to the  $\alpha_v\beta_3$   
40 integrin receptor and can thus be used particularly preferably as ligands of the  $\alpha_v\beta_3$  integrin receptor and for treating diseases in which the  $\alpha_v\beta_3$  integrin receptor is involved.

They can preferably be used to produce drugs for treating  
45 diseases in which, for example, there is excessive interaction between the  $\alpha_v\beta_3$  integrin receptor and its natural ligands.

The compounds of the formula I are preferably used for influencing metabolic processes or regulatory mechanisms underlying particular diseases, such as, for example, inhibition of angiogenesis or for treating the following diseases:

5

cardiovascular diseases such as atherosclerosis, restenosis after vessel injury, and angioplasty (neointima formation, smooth muscle cell migration and proliferation),

10 acute kidney failure,

angiogenesis-associated microangiopathies such as, for example, diabetic retinopathy or rheumatoid arthritis,

15 blood platelet-mediated vascular occlusion, arterial thrombosis,

stroke, reperfusion damage after myocardial infarct or stroke,

cancers such as, for example, in tumor metastasis or tumor growth

20 (tumor-induced angiogenesis),

osteoporosis (bone resorption after proliferation, chemotaxis and adhesion of osteoclasts to bone matrix),

25 high blood pressure, psoriasis, hyperparathyroidism, Paget's disease, malignant hypercalcemia, metastatic osteolytic lesions, inflammation, wound healing, cardiac insufficiency, CHF, and for

antiviral, antiparasitic or antibacterial therapy and prophylaxis

30 (adhesion and internalization).

The following examples illustrate the invention but the selection of these examples is non-limiting.

35 I. Synthetic examples

I.A Precursors

Preparation of the building blocks

40

Methyl (E,Z)-[5-(2-tert-butoxy-2-oxoethyl)-6-oxo-5,6-dihydro-11H-dibenzo[b,e]azepin-11-ylidene]acetate (1)

A solution of methyl (E,Z)-(6-oxo-5,6-dihydro-11H-dibenzo[b,e])-  
45 azepin-11-ylidene)acetate (27 g, 96.7 mmol) in 100 ml of DMF was added dropwise to a suspension of 4.7 g of NaH (60%; oil removed with n-pentane) in 400 ml of DMF at 0°C and stirred for about

30 min for complete formation of the anion. Then tert-butyl bromoacetate (18.9 g, 96.7 mmol) was added and the mixture was stirred at 0°C for about 1.5 h. For workup, aqueous NH<sub>4</sub>Cl solution was added to the mixture and, after concentration, the residue 5 was taken up in CH<sub>2</sub>Cl<sub>2</sub> and washed with saturated NaCl solution. Drying and concentration of the CH<sub>2</sub>Cl<sub>2</sub> phase afforded 40.5 g of solid which was then stirred with pentane and dried at 30°C in vacuo.

- 10 31.6 g; ESI-MS [M - tBu + H<sup>+</sup>] = 338;  
1H-NMR (DMSO-d<sub>6</sub>, 200 MHz) E/Z mixture: δ (ppm) 7.65-7.1 (m, 8H), 6.3/6.25 (s, 1H), 4.5 (m, 2H), 3.6 (s, 3H), 1.35 (s, 9H).

Methyl [5-(2-tert-butoxy-2-oxoethyl)-6-oxo-6,11-dihydro-5H-  
15 dibenzo[b,e]azepin-11-yl]acetate (2)

- Methyl (E,Z)-[5-(2-tert-butoxy-2-oxoethyl)-6-oxo-5,6-dihydro-11H-dibenzo[b,e]azepin-11-ylidene]acetate 1 (41 g, 104.2 mmol) was taken up in 1 l of 1:1 CH<sub>3</sub>OH/ethyl acetate and, after addition of  
20 3.1 g of catalyst (10% Pd on carbon), the mixture was hydrogenated at 50°C under a pressure of 120 bar for 21 h. Filtration through Celite, washing with CH<sub>3</sub>OH and evaporation of the combined phases afforded 41.1 g of the hydrogenation product as a white foam.

- 25 ESI-MS [M - tBu + H<sup>+</sup>] = 340.05;  
1H-NMR (DMSO-d<sub>6</sub>, 270 MHz) diastereomer mixture: δ (ppm) 7.70-7.1 (m, 8H), 4.8-4.6 (m, 3H), 3.65/3.35 (s, 3H), 3.05 (m, 2H), 1.5/1.45 (s, 9H).

- 30 11-(2-Methoxy-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]-azepin-5-yl acetate (3)

- Methyl [5-(2-tert-butoxy-2-oxoethyl)-6-oxo-6,11-dihydro-5H-  
35 dibenzo[b,e]azepin-11-yl]acetate 2 (30.5 g, 77.5 mmol) was taken up in 100 ml of CH<sub>2</sub>Cl<sub>2</sub> and, at 0°C, 150 ml of TFA were added, and the mixture was stirred at 0°C for about 1 h and then at RT. After the reaction was complete, the mixture was evaporated, and mixed with toluene 2x and again evaporated. 33.6 g of a yellowish oil  
40 were obtained as crude product; crystallization from acetone afforded 14.8 g of white solid.

- ESI-MS [M+H<sup>+</sup>] = 340;  
1H-NMR (DMSO-d<sub>6</sub>, 400 MHz) diastereomer mixture: δ (ppm) 7.7-7.05  
45 (m, 8H), 4.85-4.6 (m, 2H), 4.45 (m, 1H), 3.6/3.45 (s, 3H), 3.3 (m, 1H), 3.1/3.05 (dd, 1H).

45



bromopropionate were added dropwise and, after stirring at RT for 1 h, further KOtBu (0.2 g) and ethyl bromopropionate (0.8 g) were added. After a further 2 h, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed with H<sub>2</sub>O, dried and concentrated. Chromatography on silica 5 gel (CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH 1 to 25%) afforded 1.2 g of the required product and 2.0 g of nonreacted precursor.

ESI-MS [M+H<sup>+</sup>] = 424.15

- 10 3-[11-(2-tert-Butoxy-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo-[b,e]azepin-5-yl]propanoic acid (6)

Ethyl 3-[11-(2-tert-butoxy-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-5-yl]propanoate 5 (2.55 g, 6.02 mmol) was 15 dissolved in 15 ml of 2:1 dioxane/H<sub>2</sub>O and, after addition of 0.17 g of LiOH, stirred at RT. After the reaction was complete, the mixture was acidified with 2N HCl and, after addition of CH<sub>2</sub>Cl<sub>2</sub>, washed with saturated NaCl solution, dried and concentrated.

20

2.35 g; ESI-MS [M-tBu+H<sup>+</sup>] = 340.15;

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 200 MHz) diastereomer mixture: d (ppm) 7.75-7.05 (m, 8H), 4.8-3.8 (m, 3H), 3.5-3.1 (m, overlapped by H<sub>2</sub>O), 2.75 (m, 2H), 1.3/1.2 (s, 9H).

25

tert-Butyl [6-(4,5-dihydro-1H-imidazol-2-yl)-3-pyridinyl]methylcarbamate (trifluoroacetate) (7)

- a) tert-butyl (6-cyanopyridin-3-yl)methylcarbamate (5.0 g, 21.43 mmol) in 300 ml of CH<sub>3</sub>OH were mixed with 3.55 g of 30 sodium methanolate. After 1 h at RT, 2.6 g of ethylenediamine (hydrochloride) were added and stirred overnight. The reaction mixture was evaporated and the resulting residue was stirred with a mixture of 100 ml of CH<sub>2</sub>Cl<sub>2</sub> and 1 ml of CH<sub>3</sub>OH. 35 Insoluble solids were filtered off with suction, the filtrate was concentrated, and the residue was taken up in H<sub>2</sub>O and again washed with CH<sub>2</sub>Cl<sub>2</sub>. Evaporation of the aqueous phase afforded 5.3 g of a white solid; ESI-MS [M+H<sup>+</sup>] = 277.25.

- 40 b) 0.9 g of the Boc-protected amine in 20 ml of CH<sub>2</sub>Cl<sub>2</sub> were mixed with 10 ml of TFA and stirred at 0°C for 2 h. Evaporation of the reaction mixture afforded 1.75 g of a yellowish oil which was immediately employed further.

45

The amine required for further reaction was obtained by eliminating the Boc group with TFA (under standard conditions); the isolated TFA salts were then employed directly in the appropriate couplings.

5

tert-Butyl 1H-benzimidazol-2-ylmethylcarbamate (8)

3.32 g of a 30% NaOCH<sub>3</sub> solution were added to tert-butyl cyanomethylcarbamate (3 g; 19.21 mmol) in 20 ml of CH<sub>3</sub>OH, and the mixture was stirred at room temperature for 1 h. After addition of 3.4 g of 1,2-phenylenediamine bishydrochloride, the reaction mixture was stirred further overnight and then added to 100 ml of H<sub>2</sub>O, and the resulting solid was filtered off and dried in vacuo.

15 3.45 g; ESI-MS [M+H]<sup>+</sup> = 248.15;  
<sup>1</sup>H-NMR (270 MHz; DMSO-d<sub>6</sub>) δ (ppm) 12.60 (s, 1H), 7.30-7.15 (m 3H), 7.05 (m 2H), 4.15 (d, 2H), 1.29 (s, 9H).

The amine required for further reaction was obtained by eliminating the Boc group with TFA (under standard conditions); the isolated TFA salts were then employed directly in the appropriate couplings.

tert-Butyl 3H-imidazo[4,5-b]pyridin-2-ylmethylcarbamate (9)

25

A mixture of tert-butyl cyanomethylcarbamate (1.61 g; 10 mmol), 2,3-diaminopyridine (0.56 g; 5 mmol), N-acetylcysteine (1.68 g; 10 mmol) in 10 ml of CH<sub>3</sub>OH was heated at 50°C for 89 h. It was then concentrated, and the residue was taken up in a little CH<sub>3</sub>OH and filtered through an acidic ion exchanger (acetate on polymeric support). Renewed concentration and chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH 5%) afforded 1.09 g of the required product;

35 ESI-MS [M+H]<sup>+</sup> = 249.15  
<sup>1</sup>H-NMR (270 MHz; DMSO-d<sub>6</sub>) δ (ppm) 8.30 (m, 1H), 7.90 (m, 1H), 7.45 (m, broad, 1H), 7.20 (m 1H), 4.40 (d, 2H), 1.0 (s, 9H).

The amine required for further reaction was obtained by eliminating the Boc group with TFA (under standard conditions); the isolated TFA salts were then employed directly in the appropriate couplings.

[1-(2-Pyridinyl)-4-piperidinyl]methanamine (10)

45

- a) 1-tert-Butyloxycarbonyl-4-(aminomethyl)piperidine (14 g; 65.33 mmol; prepared as described by Prugh et al., Synthetic Communications 22 (16), 2361-2365 (1992)) was dissolved in 50 ml of THF and, at 5°C, N-methylmorpholine (6.6 g) and benzyl chloroformate (12.6 g) were added, and the mixture was stirred for about 2 h. It was then concentrated, and the residue was taken up in CH<sub>2</sub>Cl<sub>2</sub>, washed with saturated NaCl solution, dried and filtered. The residue after concentration was 23.5 g of a yellow oil which was crystallized from methyl tert-butyl ether.

18 g; ESI-MS [M+H<sup>+</sup>] = 293.15

- b) 25 ml of TFA were added to 1-tert-butyloxycarbonyl-4-(((benzyloxy)carbonyl)amino)-methyl)piperidine 10a (15 g; 43.05 mmol) in 125 ml of CH<sub>2</sub>Cl<sub>2</sub> at 0°C, and the mixture was stirred at 10°C for 20 min and then at RT. Concentration of the mixture and crystallization of the resulting residue from diethyl ether afforded 14.5 g of the free amine as TFA salt (ESI-MS [M+H<sup>+</sup>] = 249.25; melting point: 109-110°C).

5 g of the TFA salt and 2.79 g of ethyldiisopropylamine (DIPEA) in 15 ml of 2-fluoropyridine were heated to reflux. After the reaction was complete, the mixture was concentrated, and the residue was taken up in ethyl acetate and washed 4x with H<sub>2</sub>O and saturated NaCl solution. Drying, filtration and concentration afforded 4.49 g of a pale brown oil, which was crystallized from n-pentane.

4.02 g; ESI-MS [M+H<sup>+</sup>] = 362.15

- c) 3.9 g of (10b) in 150 ml of CH<sub>3</sub>OH were hydrogenated with 0.2 g of Pd (10% on carbon) under standard conditions. Filtration of the reaction mixture through Celite and concentration afforded 2.3 g;

ESI-MS [M+H<sup>+</sup>] = 192.15;

<sup>1</sup>H-NMR (270 MHz; DMSO-d<sub>6</sub>) δ (ppm) 8.1 (m, 1H), 7.5 (m, 1H), 6.8 (m, 1H), 6.55 (m, 1H), 4.3 (m, 2H), 2.7 (m, 2H), 2.45 (m, 2H), 1.75 (m, 2H), 1.5 (m, 1H), 1.05 (m, 2H).

85

1-tert-Butyloxycarbonyl-4-[(2-pyridinylamino)methyl]piperidine  
(11)

1-tert-Butyloxycarbonyl-4-(aminomethyl)piperidine (3 g; 14 mmol)  
5 and 10 ml of 2-fluoropyridine were heated to reflux for 4 h.  
Concentration and stirring of the crude product in n-pentane  
afforded 3 g of a white solid, melting point: 126-130°C;

ESI-MS [M+H+] = 292.15.

10

The amine required for further reaction was obtained by  
eliminating the Boc group with TFA (under standard conditions);  
the isolated TFA salts were then employed directly in the  
appropriate couplings.

15

N-[4-(Aminomethyl)benzyl]-2-pyridinamine (12)

a) 20 g of 2-aminopyridine were dissolved in 100 ml of CH<sub>3</sub>OH  
and, after adjustment to pH 6 with isopropanolic HCl, 36 g of  
20 p-cyanobenzaldehyde were added. 9.35 g of sodium  
cyanoborohydride were added in portions over the course of  
1 h and the mixture was stirred overnight. For workup, the  
suspension was concentrated, and the residue was taken up in  
100 ml of water and adjusted to pH > 10 with KOH. The aqueous  
25 phase was saturated with NaCl and extracted 3x with diethyl  
ether. The ether phase was filtered to remove a precipitate  
and then washed 3x with FeSO<sub>4</sub> solution, dried and  
concentrated. Purification of the residue by chromatography  
on silica gel (heptane/ethyl acetate 1:1) afforded 28.15 g of  
30 4-[(2-pyridinylamino)methyl]benzonitrile.

b) 10 g of 4-[(2-pyridinylamino)methyl]benzonitrile were  
dissolved in 280 ml of ammoniacal methanol and, after  
addition of 10 g of Raney nickel, hydrogenated for 24 h. The  
35 residue after filtration and concentration was  
chromatographed on silica gel (ethyl acetate/ethanol 1:3).

5.18 g, ESI-MS: [M+H+] = 214.

40

45

tert-Butyl [4-(1H-benzimidazol-2-yl)-1,3-thiazol-2-yl]methylcarbamate (13)

In analogy to the preparation of 8, 1.89 g of a 30% NaOCH<sub>3</sub> solution were added to tert-butyl (4-cyano-1,3-thiazol-2-yl)methylcarbamate (2.5 g; 10.45 mmol) in 25 ml of CH<sub>3</sub>OH, and the mixture was stirred at room temperature for 2 h. Addition of 1.9 g of 1,2-phenylenediamine bishydrochloride was followed by stirring overnight, and then the reaction mixture was added to 100 ml of H<sub>2</sub>O, and the solid resulting after filtration was dried in vacuo.

3.0 g; ESI-MS: [M+H]<sup>+</sup> = 331.15,

<sup>1</sup>H-NMR (400 MHz; DMSO-d<sub>6</sub>) δ (ppm) 8.25 (s, 1H), 7.95 (m, 1H), 7.65 (m, 1H), 7.55 (m, 1H), 7.2 (m, 2H), 4.55 (m, 2H), 1.45 (s, 9H).

The amine required for further reaction was obtained by eliminating the Boc group with TFA (under standard conditions); the isolated TFA salts were then employed directly in the appropriate couplings.

Di(tert-butyl) 4-(1H-benzimidazol-2-yl)benzylimidodicarbonate (14)

Di(tert-butyl) 4-cyanobenzylimidodicarbonate (10 g; 30.1 mmol) was dissolved in 200 ml of pyridine and, after addition of 45 ml of triethylamine, H<sub>2</sub>S was passed in at 0°C for 1.5 h and the mixture was kept at RT overnight. The reaction mixture was concentrated in vacuo and coevaporated with toluene twice. Stirring of the resulting residue in diethyl ether afforded 8.5 g of white solid.

The thioamide (6 g; 16.37 mmol) was suspended in 40 ml of CH<sub>2</sub>Cl<sub>2</sub> and, after addition of 22.3 g of CH<sub>3</sub>I, stirred at RT overnight. The mixture was then evaporated, taken up in 20 ml of CH<sub>3</sub>OH and, after addition of 1,2-phenylenediamine (1.95 g; 18.01 mmol), again stirred at RT overnight. Concentration of the mixture afforded 6.9 g of yellow solid.

ESI-MS [M+H]<sup>+</sup> = 424.25;

The amine required for further reaction was obtained by eliminating the Boc group with TFA (under standard conditions); the isolated TFA salts were then employed directly in the appropriate couplings.

[5-(2-Methoxy-2-oxoethyl)-11-oxo-5,11-dihydro-10H-dibenzo-  
[b,e][1,4]diazepin-10-yl]acetic acid (37)

- 5 a) A mixture of 5,10-dihydro-11H-dibenzo[b,e][1,4]diazepin-11-one (10 g; 47.6 mmol; preparation as described in Pharmazie 45, 1990, 555-559), 100 g of methyl bromoacetate, 0.5 g of KI and 180 ml of DMF was heated at 60°C for 110 h. Concentration of the mixture, chromatography of the crude product on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH 3 → 5%) and
- 10 crystallization of the resulting oil from ethyl acetate afforded 7.1 g of gray solid; ESI-MS [M+H<sup>+</sup>] = 283
- <sup>1</sup>H-NMR (400 MHz; DMSO-d<sub>6</sub>): δ (ppm) 10.3 (s, 1H), 7.65 (d, 2H), 7.45 (m, 2H), 7.05-7.2 (m, 4H), 4.75 (d, 2H), 3.6 (s, 3H).
- 15 b) A solution of methyl (11-oxo-10,11-dihydro-5H-dibenzo[b,e][1,4]diazepin-5-yl)acetate 37a (7 g; 24.8 mmol) in 40 ml of DMF was added dropwise to a suspension of 1.3 g of NaH (60%; oil removed with n-pentane) in 10 ml of DMF at 5°C, and the mixture was stirred for about 30 min to complete formation of
- 20 the anion. Then tert-butyl bromoacetate (5.4 g, 27.7 mol) was added dry and the mixture was stirred at 10°C for about 2 h. For workup, the mixture was mixed with H<sub>2</sub>O, diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed with saturated NaCl solution. Drying and
- 25 concentration of the CH<sub>2</sub>Cl<sub>2</sub> phase afforded a black oil, which was purified by chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH 2 → 10%); 7.8 g; ESI-MS [M - tBu + H<sup>+</sup>] = 341
- 30 c) tert-Butyl [5-(2-methoxy-2-oxoethyl)-11-oxo-5,11-dihydro-10H-dibenzo[b,e][1,4]diazepin-10-yl]acetate 37b (7.8 g; 19.67 mmol) in 15 ml of CH<sub>2</sub>Cl<sub>2</sub> was mixed with 10 ml of TFA and stirred at RT for 2 h. Concentration of the mixture and drying afforded 7.4 g of brown solid; ESI-MS [M + H<sup>+</sup>] = 341
- 35

N-[4-(Aminomethyl)-1,3-thiazol-2-yl]-N'-benzylurea  
(hydrochloride) (38)

- 40 a) A solution of 123 g of pyridinium bromide perbromide in 600 ml of THF was slowly added dropwise to 2-(2-oxopropyl)-1H-isoindole-1,3(2H)-dione (70 g; 0.345 mol) in 600 ml of THF, and the mixture was then stirred for about 3 h. For workup, the precipitated solids were filtered off, and the mother liquor was concentrated, taken up in ethyl acetate and
- 45 thoroughly washed with aqueous bisulfite solution. Drying and concentration afforded 150 g of a yellow oil, which was stirred with methyl tert-butyl ether.

63.4 g; m.p.: 142 to 143°C; ESI-MS  $[M+H^+] = 283.95$

- b) 2-(3-Bromo-2-oxopropyl)-1*H*-isoindole-1,3(2*H*)-dione 38a (6 g; 21.27 mmol) and thiourea (2 g; 26.27 mmol) were stirred in 70 ml of THF at RT for about 2 h. The resulting precipitate was filtered off with suction and dried. 5 g; ESI-MS  $[M+H^+] = 260.05$
- c) 2-[(2-Amino-1,3-thiazol-4-yl)methyl]-1*H*-isoindole-1,3(2*H*)-dione hydrobromide 38b (4.5 g; 13.23 mmol), benzyl isocyanate (1.8 g, 13.52 mmol) and 1.7 g of DIPEA were heated to reflux in 50 ml of toluene. After the reaction was complete, the mixture was evaporated, and the residue was taken up in  $CH_2Cl_2$  and washed with 1 N HCl, saturated  $NaHCO_3$  and NaCl solutions. Drying and concentration afforded 4.7 g of orange solid, which was recrystallized from  $CH_3OH$ . 3.0 g; ESI-MS  $[M+H^+] = 393.05$
- $^1H$ -NMR (360 MHz, DMSO)  $\delta$  ppm: 10.65 (s, 1H), 7.9 (m, 4H), 7.25 (m, 5H), 6.85 (s, 1H), 4.7 (s, 2H), 4.35 (d, 2H),
- d) *N*-Benzyl-*N'*-(4-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-methyl]-1,3-thiazol-2-yl)urea 38c (3 g; 7.64 mmol) was suspended in 50 ml of  $CH_3OH$  and, after addition of 2 g of hydrazine hydrate, stirred at RT for 2 h. The resulting solids were filtered off, and the resulting mother liquor was evaporated and stirred with 0.5 N HCl. Renewed filtration and evaporation of the mother liquor led to a concentration of the required product, and thus this purification step was repeated 3 x. 0.78 g; ESI-MS  $[M+H^+] = 263.05$
- [4-(Aminomethyl)-1,3-thiazol-2-yl]guanidine (bishydrochloride) (39)
- a) 2-(3-Bromo-2-oxopropyl)-1*H*-isoindole-1,3(2*H*)-dione 38a (10 g; 35.45 mmol) and 2-iminothiobiuret (4.6 g; 38.99 mmol) were stirred in 150 ml of THF at RT for about 2 d. The resulting precipitate was filtered off with suction and dried; 11.4 g; ESI-MS  $[M+H^+] = 302.15$ .
- b) 5 g of 39a were treated with hydrazine hydrate in  $CH_3OH$  in analogy to 38d. Stirring of the resulting crude product with 0.5 N HCl and subsequently with ethanol afforded 3.16 g; ESI-MS  $[M+H^+] = 172.05$ .

## N-[4-(Aminomethyl)benzyl]-N'-benzylurea (40)

340 mg (2.5 mmol) of diamino-p-xylene were introduced into 15 ml of acetonitrile and cooled to 0 to 5°C and, over the course of 5 min, 0.29 ml of benzyl isocyanate was added and the mixture was then stirred at RT for 16 h. The resulting suspension was added to water, and the precipitate was filtered off with suction, washed with water and dried (402 mg). ESI-MS [M+H<sup>+</sup>] = 270.

## 10 N-[3-(Aminomethyl)phenyl]-N'-benzylurea (hydrochloride) (41)

a) 4.7 g (25 mmol) of m-nitrobenzylamine were added to 250 ml of CH<sub>2</sub>Cl<sub>2</sub> and, after addition of 1.36 ml of DIPEA, the mixture was refluxed until the benzylamine had dissolved. The solution was cooled to 0°C, and di-tert-butyl carbonate (1.1 eq.) was added dropwise. The mixture was then stirred at RT for 16 h, and subsequently the solution was extracted with water and saturated NaHCO<sub>3</sub> solution. The organic phase was dried and concentrated, and the resulting residue was 20 crystallized from 30 ml of diethyl ether (5.07 g).

b) 4.69 g of the above nitro compound were dissolved in 50 ml of ethanol and hydrogenated with 460 mg of 5% Pd on active carbon under atmospheric pressure. The reaction was complete after 2 h. The filtrate after filtration was concentrated, and the remaining oil was immediately reacted further (3.80 g).

c) The oil was dissolved in 100 ml of THF, and 3.66 ml of DIPEA and then dropwise 2.60 g of benzyl isocyanate were added to the solution. The mixture was stirred at RT for 16 h, then under reflux for 6 h and then at RT for a further 16 h. It was concentrated and crystallized from 30 ml of ethyl acetate, and the resulting precipitate was filtered off with suction and dried; 4.90 g; ESI-MS [carbamic acid fragment + H<sup>+</sup>] = 300.

d) The Boc compound was dissolved in 20 ml of THF, and 5 ml of HCl in diethyl ether (saturated at 0°C) were added. After 1 h, a further 15 ml of HCl in diethyl ether were added and the mixture was stirred for 16 h. The precipitate which had formed was filtered off with suction, washed with THF and diethyl ether and dried (3.72 g). ESI-MS [M+H<sup>+</sup>] = 256.

## 45 3-Amino-N-(1H-imidazol-2-yl)propanamide (42)



a) Z- $\beta$ -alanine (10 g; 44.8 mmol) was dissolved in 200 ml of DMF, and 15.86 g (3.5 eq) of N-methylmorpholine and 5.9 g (0.5 eq) of 2-aminoimidazole sulfate were added. At  $-10^{\circ}\text{C}$ , 7.87 g (1.3 eq) of HOBT and 11.16 g (1.3 eq) of N'-(dimethylamino-propyl)-N-ethylcarbodiimide were added, and the mixture was stirred for 1 h while warming to RT and then for 18 h. 150 ml of diethyl ether were added, whereupon a white solid precipitated and was filtered off with suction. The residue was washed with cold diethyl ether and suspended in ethyl acetate, and 1 N HCl was added until the reaction was acidic. The aqueous solution was extracted 1 x with ethyl acetate, and then the aqueous phase was adjusted to a basic pH with 10% NaOH at  $4^{\circ}\text{C}$ . The resulting precipitate was filtered off with suction and washed with water. 5.4 g; ESI-MS  $[M+H]^+$  = 289.05.

b) 5.3 g of the Z compound 42a were suspended in 250 ml of ethanol, and 530 mg of 10% Pd on active carbon were added. The mixture was hydrogenated with  $\text{H}_2$  at RT for 18 h and then diluted with  $\text{CH}_3\text{OH}$ , and the suspension was boiled to dissolve the product precipitate. Filtration and concentration of the solution afforded 1.5 g; ESI-MS  $[M+H]^+$  = 155.05.

4-(Aminomethyl)-N-benzylpiperidine-1-carboxamide (43)

a) Benzyl 4-(aminomethyl)-1-piperidinecarboxylate (trifluoroacetate) (4 g; 11.04 mmol; preparation as described in 10b) was suspended in 60 ml of toluene and heated with 1.43 g of DIPEA and benzyl isocyanate (1.62 g, 12.14 mmol) to reflux for 4 h. After evaporation of the reaction mixture, the residue was taken up in  $\text{CH}_2\text{Cl}_2$  and extracted 2 x each with 1 N HCl and saturated NaCl solutions, and the organic phase was dried and concentrated. 4.2 g; ESI-MS  $[M+H]^+$  = 382.25.

b) 4 g of benzylurea 43a were dissolved in a 3:1 ethyl acetate/ $\text{CH}_3\text{OH}$  mixture with heating and, after addition of 0.2 g of 10% Pd on active carbon, hydrogenated under standard conditions at 35 to  $40^{\circ}\text{C}$ . After the reaction was complete, the mixture was filtered through Celite and evaporated. 2.8 g; ESI-MS  $[M+H]^+$  = 248.15.

$^1\text{H-NMR}$  (400 MHz, DMSO)  $\delta$  ppm: 7.4-7.15 (m, 11H), 7.05 (t, 1H), 5.08 (s, 2H), 4.25 (d, 2H), 3.95 (d, 2H), 2.8 and 2.65 (each m, 2H), 1.6 (m, 3H), 0.95 (m, 2H).

[4-(1*H*-Benzimidazol-2-yl)-thien-2-yl]methanamine  
(trifluoroacetate) (44)

The *tert*-butyl-(4-cyanothien-2-yl)methylcarbamate used as  
5 precursor was prepared by standard methods from 5-(aminomethyl)-  
3-thiophenecarbonitrile (WO 98/06741).

- 10 a) 3.6 g of a 30% NaOCH<sub>3</sub> solution were added to *tert*-butyl  
(4-cyanothien-2-yl)methylcarbamate (5 g; 20.98 mmol) in 70 ml  
of CH<sub>3</sub>OH and the mixture was stirred at room temperature for  
2 h. Addition of 3.6 g of 1,2-phenylenediamine  
bishydrochloride was followed by stirring overnight, and then  
the reaction mixture was added to 50 ml of H<sub>2</sub>O and extracted  
15 with CH<sub>2</sub>Cl<sub>2</sub>. Drying and concentration of the organic phase  
afforded 4.3 g of a yellow solid, which was purified by  
chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH 1 → 10%).  
1.6 g; ESI-MS: [M+H<sup>+</sup>] = 333.15.
- 20 b) 1.5 g of the Boc compound 44a were dissolved in 10ml of CH<sub>2</sub>Cl<sub>2</sub>  
and, after addition of 15 ml of TFA at 0°C, stirred at room  
temperature for 2 h. Evaporation of the reaction mixture and  
stirring with *n*-pentane afforded 1.5 g of the amine as  
trifluoroacetate.

25 [5-(1*H*-Benzimidazol-2-yl)thien-2-yl]methanamine (45)

Preparation took place in analogy to 44 starting from  
5-(aminomethyl)thiophene-2-carbonitrile (preparation as described  
in WO 95/23609). The crude product obtained after TFA cleavage  
30 was dissolved in water and extracted 2x with diethyl ether, and  
the aqueous phase was adjusted to pH 10-11 and then extracted 2x  
with ethyl acetate. The aqueous phase was saturated with NaCl and  
again extracted with ethyl acetate. The combined organic phases  
were dried and concentrated (6.3 g); ESI-MS [M+H<sup>+</sup>] = 230.1.

35 2-(Piperidin-4-ylamino)pyridine (46)

- 40 a) Ethyl 4-amino-1-piperidinecarboxylat (6 g, 34.8 mmol) and  
25 g of 2-fluoropyridine were refluxed for 48 h. The solid  
formed after cooling was filtered off with suction, stirred  
with *n*-pentane and dried; 6.26 g of yellow powder;  
ESI-MS [M+H<sup>+</sup>] = 250.15.
- 45 b) 6 g of ethyl 4-(pyridin-2-ylamino)piperidine-1-carboxylate  
46a were refluxed in 30 ml of 47% HBr for 6 h. Evaporation of  
the mixture, stirring of the resulting crude product with

ethyl acetate/CH<sub>3</sub>OH (9:1) and renewed drying afforded 7.1 g of white solid; ESI-MS [M+H<sup>+</sup>] = 178.15.

N-[4-(Aminomethyl)phenyl]-1H-benzimidazole-2-amine  
5 (hydrochloride) (47)

- 10 a) 20 g of tert-butyl 4-aminobenzylcarbamate (89.97 mmol) - dissolved in 100 ml of CH<sub>3</sub>CN - were added dropwise to a solution of 24.5 g of thiocarbonyldiimidazole and 1.56 g of imidazole in 600 ml of CH<sub>3</sub>CN at 0°C, and the mixture was stirred at RT overnight. Then 19.5 g of 1,2-phenylenediamine were added and the mixture was again stirred at RT for 2 h. For work up, the reaction mixture was evaporated in vacuo, and the residue was taken up in CH<sub>2</sub>Cl<sub>2</sub>, washed 7x with 10% citric acid solution and 2x with saturated NaCl solution, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The crude product obtained in this way (31.78 g; brown foam) was immediately reacted without further purification; ESI-MS [M+H<sup>+</sup>] = 373.15.

20 <sup>1</sup>H-NMR (360 MHz, DMSO) δ ppm: 9.5 and 9.05 (each s, 1H), 7.45 (d, 2H), 7.35 (m, 1H), 7.20 (d, 1H), 7.15, 6.95, 6.75, 6.60 (each m, 1H), 4.85 (s, 2H), 4.10 (d, 2H), 1.35 (s, 9H).

- 25 b) The crude product 47a was dissolved together with 36.7 g of HgO (yellow) and 0.4 g of sulfur in 750 ml of ethanol and refluxed for 2 h. The reaction mixture was then filtered twice through Celite and evaporated to dryness; 20.7 g, ESI-MS [M+H<sup>+</sup>] = 339.15.

- 30 c) 7 g of the crude product 47b were introduced into 70 ml of CH<sub>2</sub>Cl<sub>2</sub> and, after addition of 35 ml of HCl in diethyl ether (saturated at 0°C), stirred at RT for 2 h. The resulting precipitate was filtered off with suction, washed with CH<sub>2</sub>Cl<sub>2</sub> and dried.

35 6.7 g of brown amorphous solid; ESI-MS [M+H<sup>+</sup>] = 239.15

40 <sup>1</sup>H-NMR (360 MHz, DMSO) δ ppm: 11.6 (s broad, 1H), 8.4 (s broad, 3H), 8.25 (s broad, 1H), 7.65 and 7.55 (each d, 2H), 7.45 and 7.3 (each m, 2H), 4.19 (m, 2H).

N<sup>1</sup>-(1H-Benzimidazol-2-yl)pentane-1,5-diamine (hydrochloride) (48)

Preparation took place in analogy to the synthesis of 47 starting from 7 g of N-Boc-1,5-diaminopentane hydrochloride (29.3 mmol). After reaction in analogy to 47a, 10.3 g of N-Boc-5-[[[(2-aminoanilino)carbothioyl]amino]pentan-1-amine were

obtained; ESI-MS  $[M+H]^+ = 353.25$ . Cyclodesulfurization and subsequent elimination of the Boc group with TFA afforded an oily crude product, which was taken up in  $CH_3OH$  and converted into the corresponding hydrochloride with 250 ml of ethereal  $HCl$

5 (saturated at  $0^\circ C$ ). Stirring of the resulting solids with a  $CH_3OH$ /methyl tert-butyl ether mixture afforded 1.8 g of a reddish amorphous solid.

$^1H$ -NMR (360 MHz, DMSO)  $\delta$  ppm: 9.30 (t, 1H), 8.15 (s broad, 3H),  
10 7.40 and 7.25 (each m, 2H), 3.35 (m, 2H overlapped by  $H_2O$  peak),  
2.80 (m, 2H), 1.65 (m, 4H), 1.45 (m, 2H).

$N^1$ -(1H-Benzimidazol-2-yl)butane-1,4-diamine (trifluoroacetate)  
(49)

15

Preparation took place in analogy to the preparation of compound 47 starting from 9.87 g of N-Boc-1,4-diaminobutane (52.3 mmol). After reaction in analogy to 49a, 17.08 g of N-Boc-4-{{(2-aminoanilino)carbothioyl}amino}butan-1-amine were

20 obtained; ESI-MS  $[M+H]^+ = 338.99$ .

Subsequent cyclodesulfurization and Boc elimination with TFA afforded a brown solid, which was stirred several times with n-pentane and then recrystallized from a  $CH_3OH$ /methyl tert-butyl ether mixture; 14.35g, ESI-MS  $[M+H]^+ = 205.15$ .

25

$^1H$ -NMR (360 MHz, DMSO)  $\delta$  ppm: 9.20 (t, 1H), 7.80 (s broad, 3H),  
7.35 and 7.20 (each m, 2H), 3.40 (m, 2H partially overlapped by  $H_2O$  peak),  
2.80 (m, 2H), 1.65 (m, 4H).

30 N-(Piperidin-4-ylmethyl)-1H-benzimidazol-2-amine (trifluoroacetate) (50)

a) A solution of

tert-butyloxycarbonyl-4-(aminomethyl)-1-piperidine (5.39 g;  
35 25 mmol) in 25 ml of  $CH_3CN$  was added dropwise to 6.75 g of thiocarbonyldiimidazole and 0.5 g of imidazole in 100 ml of  $CH_3CN$  at  $0^\circ C$ , and the mixture was stirred at RT for 3 h. Then 1,2-phenylenediamine (5.5 g; 50.86 mmol) was added and the mixture was heated at  $60^\circ C$  for about 1 h. The solid resulting  
40 on cooling was filtered off with suction and dried.  
6.79 g; ESI-MS  $[M+H^+-tBu] = 309.15$ .

b) tert-Butoxycarbonyl-4-{{(2-aminoanilino)carbothioyl}-amino}methyl-1-piperidine 50a (5 g; 13.72 mmol), 5.94 g of  
45  $HgO$  (yellow) and 0.6 g of sulfur in 150 ml of ethanol were

refluxed for 1 h. The mixture was filtered 2x through Celite and evaporated, and the resulting crude product was purified by chromatography on silica gel ( $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$  5  $\rightarrow$  25 %). 2.65 g; ESI-MS  $[\text{M}+\text{H}^+] = 331.25$ .

5

$^1\text{H}$ -NMR (360 MHz, DMSO)  $\delta$  ppm: 7.15 and 6.9 (each m, 2H), 3.95 (d, 2H), 3.2 (m 2H), 2.7 (br m; 2H), 1.8 (m, 1H), 1.7 (m, 2H), 1.35 (s, 9H), 1.05 (m, 2H).

- 10 c) *tert*-Butyloxycarbonyl-4-[(1*H*-benzimidazol-2-ylamino)methyl]-1-piperidine 50b (2.65 g; 8.02 mmol) were treated with 10 ml of TFA under standard conditions. Concentration and stirring of the crude product with *n*-pentane afforded 2.3 g; ESI-MS  $[\text{M}+\text{H}^+] = 231.15$ .

15

$^1\text{H}$ -NMR (360 MHz, DMSO)  $\delta$  ppm: 13.25 (s, 1H), 9.35 (m, 1H), 8.8 and 8.5 (each br s, 1H), 7.4 and 7.20 (each m, 2H), 3.3 (m, 4H), 2.85 (m, 2H), 1.9 (m, 3H), 1.35 (m, 2H).

- 20 N-[4-(Aminomethyl)-1,3-thiazol-2-yl]pyridin-2-amine (bishydrochloride) (51)

- a) 2-Aminopyridine (11 g; 116.9 mmol) and benzyl isothiocyanate (21 g; 128.7 mmol) were refluxed in 250 ml of acetone for 3 h. The mixture was then evaporated and the resulting residue was stirred first with acetone/*n*-pentane and then only with *n*-pentane. 21.4 g; ESI-MS  $[\text{M}+\text{H}^+] = 258.05$ .

- 30 b) *N*-Benzoyl-*N'*-pyridin-2-ylthiourea 51a (5 g; 19.43 mmol) was introduced into 100 ml of an acetone/ $\text{CH}_3\text{OH}$  mixture. 1.34 g of  $\text{K}_2\text{CO}_3$  in 5 ml of  $\text{H}_2\text{O}$  were added and the mixture was refluxed for 2 h. For workup, the precipitate which had formed was filtered off, the mother liquor was evaporated, and the resulting residue was added to  $\text{H}_2\text{O}$ . Extraction with  $\text{CH}_2\text{Cl}_2$ , drying and evaporation of the organic phases afforded 5.4 g; ESI-MS  $[\text{M}+\text{H}^+] = 154.05$ .

40  $^1\text{H}$ -NMR (270 MHz, DMSO- $d_6$ )  $\delta$  ppm: 10.65 (s, 1H), 10.55 (s, 1H), 8.9 (s, 1H), 8.25, 7.75, 7.20, 7.10 (each m, 1H).

- c) *N*-Pyridin-2-ylthiourea 51b (5 g; 35.9 mmol) and 2-(3-bromo-2-oxopropyl)-1*H*-isoindole-1,3(2*H*)-dione (9.1 g; 32.26 mmol) were stirred in 500 ml of THF at RT for 2 h. The precipitate which had formed was filtered off and dried. 45 12.3 g of white solid; ESI-MS  $[\text{M}+\text{H}^+] = 337.05$ .

- d) Elimination of the phthaloyl group was carried out analogously starting from 2-([2-(pyridin-2-ylamino)-1,3-thiazol-4-yl]methyl)-1*H*-isoindole-1,3(2*H*)-dione 51c (10 g; 23.96 mmol) with 7 g of hydrazine hydrate in 250 ml of CH<sub>3</sub>OH. Subsequent workup afforded 4.15 g of yellow solids; ESI-MS [M+H<sup>+</sup>] = 207.05.

N-[5-(Aminomethyl)-1,3-thiazol-2-yl]pyridin-2-amine (bishydrochloride) (52)

10

Preparation took place in analogy to 51 using 2-chloro-3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)propanal (preparation described in *THL* 39 (1998), 8085-8088). After cleavage of the phthaloyl group with hydrazine hydrate under standard conditions and stirring the crude product with CH<sub>2</sub>Cl<sub>2</sub>, 1.12 g of yellow solids were obtained; ESI-MS [M+H<sup>+</sup>] = 207.05.

N-[5-(Aminomethyl)-1,3-thiazol-2-yl]guanidine (dihydrochloride) (53)

20

- a) 31 g (130 mmol) of 2-chloro-3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)propanal (preparation described in *THL* 39 (1998), 8085-8088) and 15.4 g of amidinothiourea were heated in 200 ml of *n*-butanol at 110°C for 75', and then the mixture was evaporated and the residue was mixed with CH<sub>2</sub>Cl<sub>2</sub> and concentrated NH<sub>3</sub>. Evaporation of the organic phase, purification of the residue by chromatography on silica gel ((CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH 0 to 5 %) and crystallization from acetone afforded 12.3 g of N-[5-([1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]-1,3-thiazol-2-yl]guanidine.

- b) 1 g of 53a in 20 ml of CH<sub>3</sub>OH was mixed with 0.81 ml of hydrazine hydrate and stirred at RT for 2 h. The mixture was then cooled to 0°C and filtered, and the filtrate was concentrated and stirred with dilute HCl. This procedure was repeated several times, and the crude product obtained in this way was then stirred with ethanol; 0.92 g of white solids, ESI-MS [M+H<sup>+</sup>] = 172.05.

40 *tert*-Butyl 2-[4-(1*H*-benzimidazol-2-yl)phenyl]ethylcarbamate (54)

Preparation took place in analogy to the synthesis of building block 14 starting from *tert*-butyl

2-(4-cyanophenyl)ethylcarbamate. The crude product obtained after reaction with H<sub>2</sub>S, alkylation with CH<sub>3</sub>I and reaction with

1,2-phenylenediamine was purified by chromatography on silica gel ( $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$  4 to 50%) (4.8 g); ESI-MS  $[\text{M}+\text{H}^+] = 338.15$ .

→ the amine required for the subsequent reaction was obtained by eliminating the Boc group with TFA (under standard conditions); the isolated TFA salts were then employed directly in the appropriate couplings.

N-([5-(Aminomethyl)thien-3-yl]methyl)pyridin-2-amine  
10 (trifluoroacetate) (55)

a) A solution of tert-butyl (4-cyanothien-2-yl)methylcarbamate (7 g; 29.4 mmol) in 120 ml of ethanol was saturated with  $\text{NH}_3$  and then hydrogenated in the presence of Ra-Ni (9 g of aqueous suspension; decanted with ethanol) under standard conditions. Filtration of the reaction mixture, evaporation and chromatography of the resulting residue on silica gel ( $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$  plus aqueous  $\text{NH}_3$ ) afforded 4.4 g of the amine as yellowish oil.

20

b) 1.2 g of the amine 55a (4.3 mmol), 0.6 g of ethyldiisopropylamine and 15 g of 2-fluoropyridine were refluxed for 20 h. The residue obtained after evaporation of the mixture was taken up in  $\text{CH}_2\text{Cl}_2$ , washed with 0.1N HCl and saturated NaCl solutions, dried and again evaporated. 1 g; ESI-MS  $[\text{M}+\text{H}^+] = 320.15$ .

25

c) 0.9 g of the Boc-protected amine 55b were dissolved in 10 ml of  $\text{CH}_2\text{Cl}_2$  and, after addition of 5 ml of TFA at  $0^\circ\text{C}$ , stirred at room temperature for 1 h. Evaporation of the reaction mixture afforded 1.65 g of a brownish oil, which was reacted directly without further purification (ESI-MS  $[\text{M}+\text{H}^+] = 220.05$ ).

30

35  $\text{N}^1$ -Methyl- $\text{N}^2$ -pyridin-2-ylethane-1,2-diamine (acetate) (56)

a) tert-Butyl 2-aminoethyl(methyl)carbamate (2.8 g; 16.1 mmol) and 19 ml of 2-fluoropyridine were refluxed for about 23 h. Evaporation of the reaction mixture afforded 4 g of a brown oil (ESI-MS  $[\text{M}+\text{H}^+] = 252.15$ ) which was directly reacted further.

40

b) 2 g of the crude product 56a were stirred in 30 ml of TFA at RT overnight. The mixture was evaporated and purified by MPLC on RP silica gel ( $\text{CH}_3\text{CN}/\text{H}_2\text{O}$  plus 0.1% acetic acid); 2.2 g; ESI-MS  $[\text{M}+\text{H}^+] = 152.1$ .

45

## N-[4-(Aminomethyl)phenyl]-2-pyridinamine (57)

Preparation took place in analogy to 56 starting from tert-butyl 4-aminobenzylcarbamate. 38 mg of the title compound were isolated; ESI-MS  $[M+H^+] = 200.15$ .

## N-[4-(Aminomethyl)phenyl]-N'-benzylurea (trifluoroacetate) (58)

- a) Triethylamine (6.8 g, 67.12 mmol) and then, at 0°C, di-tert-butyl dicarbonate (18.6 g, 85.00 mmol) were added to 4-aminobenzylamine (10.0 g, 81.85 mmol) in 150 ml of  $CH_2Cl_2$ . The mixture was stirred at 0°C for 1 h and at RT for 2 h. For workup, 150 ml of a 1% aqueous citric acid solution were added, the phases were separated, and the aqueous phase was back-extracted twice with  $CH_2Cl_2$  (150 ml). Renewed washing with  $H_2O$ , drying of the combined organic phases with  $Na_2SO_4$  and evaporation afforded a solid which was stirred with a little diisopropyl ether, filtered off with suction and dried.
- 13.0g; ESI-MS  $[M+H^+-tBu] = 167.05$ .
- $^1H$ -NMR (360 MHz,  $CDCl_3$ )  $\delta$  (ppm): 7.04 (2H, d), 6.61 (2H, d), 4.78 (1H, s br.), 4.17 (2H, d), 3.67 (2H, s br.), 1.46 (9H, s).
- b) Benzyl isocyanate (2.40 g, 18.00 mmol) was added to a solution of the protected amine 58a (4.0 g, 17.99 mmol) and triethylamine (1.82 g, 18.00 mmol) in 220 ml of 10:1 toluene/DMF while cooling in ice. The reaction mixture was stirred at RT overnight. It was possible for part of the urea which had formed to be filtered off directly as precipitate and dried. The filtrate was washed twice with  $H_2O$ , dilute tartaric acid to pH 3 and again twice with  $H_2O$  to pH 5, and the organic phase was then dried and evaporated. A total of 6.0 g was obtained in this way; ESI-MS  $[M+H^+-tBu] = 300.15$ .
- c) The urea 58b obtained in this way was introduced into 90 ml of  $CH_2Cl_2$  and, at 0°C, TFA (2.24 g, 196.25 mmol) - dissolved in 90 ml of  $CH_2Cl_2$  - was added dropwise. After 3 h, a further 1 ml of TFA was added, and the mixture was then stirred at RT overnight. Addition of a further 1 ml of TFA was followed by stirring for 5 h, and then the mixture was poured into ice-water and extracted with ethyl acetate (2 x 50 ml). The aqueous phase was basified with 2N NaOH solution and extracted with  $CH_2Cl_2$  (2 x 50 ml). The insoluble portion between the phases was filtered off and dried.



4 g; ESI-MS  $[2M+H^+] = 511.35$ .

$^1H$ -NMR (200 MHz, DMSO)  $\delta$  (ppm): 8.52 (1H, s), 7.39-7.07 (9H, m), 6.62 (1H, t), 4.27 (2H, d), 3.61 (2H, s).

5

[4-(Aminomethyl)phenyl]guanidine (bishydrochloride) (59)

p-Aminobenzylamine (6.7 g; 54.84 mmol) was suspended in 20 ml of 6N HCl and, while refluxing, 5.3 g of cyanamide - dissolved in 10 5 ml of  $H_2O$  - were slowly added dropwise. After the reaction was complete, 50% NaOH solution was added to the solution at  $0^\circ C$ , and the resulting precipitate was filtered off with suction, boiled in 50 ml of ethanol and filtered. Concentration of the mother liquor and stirring of the resulting residue with diethyl ether 15 afforded 1.4 g of yellow solid; m.p.:  $255^\circ C$ .

[4-(5-Chloro-1H-benzimidazol-2-yl)phenyl]methanamine (trifluoroacetate) (60)

20 Preparation took place in analogy to building block 14 by reaction with 4-chloro-1,2-diaminobenzene (104 mg); ESI-MS  $[M+H^+]$ : 258.05, 129.6.

[4-(5,6-Dimethyl-1H-benzimidazol-2-yl)phenyl]methanamine (trifluoroacetate) (61) 25

Preparation took place in analogy to building block 14 by reaction with 4,5-diamino-o-xylene (230 mg); ESI-MS  $[M+H^+]$ : 253.1, 252.1, 147.1, 126.6.

30

N-[2-(4-Piperidinyl)ethyl]-2-pyridinamine (tristrifluoroacetate) (62)

Synthesis took place in analogy to building block 56 starting 35 from 2-(4-piperidinyl)ethanamine which was previously converted under standard conditions into the corresponding tert-butyl 2-(4-piperidinyl)ethylcarbamate. 251 mg of the title compound were isolated; ESI-MS  $[M-3CF_3COO^-+H^+]$ : 206.1, 103.7.

40 N-[2-(3-Pyrrolidinyl)ethyl]-2-pyridinamine (tristrifluoroacetate) (63)

Synthesis took place in analogy to building block 56 starting from 2-(3-pyrrolidinyl)ethanamine which was previously converted 45 under standard conditions into the corresponding tert-butyl

2-(3-pyrrolidinyl)ethylcarbamate. 500 mg of the title compound were isolated; ESI-MS  $[M-3CF_3COO^-+H^+]$ : 192.15.

{4-[(3-Phenylpropanoyl)amino]phenyl}methanamine (hydrochloride) (64)

- a) 350 mg (1.66 mmol) of 3-phenylpropionic acid were dissolved in 20 ml of THF and, at 0°C, 1.24 g of DIPEA and 2.3 ml of 50% propanephosphonic anhydride solution in THF were added. After 15 min, 350 mg (1.57 mmol) of tert-butyl 4-aminobenzylcarbamate in 5 ml of THF were added dropwise, and the mixture was warmed to RT and stirred for 16 h. It was concentrated, the residue was taken up in 70 ml of H<sub>2</sub>O/ethyl acetate, and the organic phase was washed with saturated NaHCO<sub>3</sub> solution, 1% citric acid and H<sub>2</sub>O, dried and concentrated (500 mg); ESI-MS  $[M+H^+-t-butyl]$  = 299.
- b) 880 mg (2.48 mmol) of the above compound were dissolved in 20 ml of THF, and about 20 ml of HCl in diethyl ether (saturated at 0°C) were added. The solution was then stirred at RT for 2 d and the resulting precipitate was filtered off and dried (700 mg); ESI-MS  $[M+H^+-NH_4^+]$  = 234.

(4-[(Benzyloxy)carbonyl]amino}phenyl}methanamine (hydrochloride) (65)

- a) 730 mg (3.28 mmol) of tert-butyl 4-aminobenzylcarbamate were dissolved in 20 ml of THF and, after addition of a solution of 1.18 g of NaHCO<sub>3</sub> in 10 ml of water, cooled to 0°C. 590 mg of benzyloxycarbonyl chloride were added dropwise to this mixture, and it was stirred at RT overnight. The residue after concentration was dissolved in 70 ml of H<sub>2</sub>O/ethyl acetate, and the organic phase was separated off and washed with saturated NaHCO<sub>3</sub> solution, 1% citric acid and H<sub>2</sub>O. Drying and concentration afforded 1.08 g; ESI-MS  $[M+Na^+]$  = 379.
- b) The product from the previous stage was dissolved in 10 ml of THF, and in 20 ml of HCl in diethyl ether (saturated at 0°C) were added. The solution was stirred overnight, and the resulting crystals were filtered off with suction (800 mg); ESI-MS  $[M+H^+-NH_3]$  = 240.

[11-(2-tert-Butoxy-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-5-yl]acetic acid (66)

Alkylation of tert-butyl (6-oxo-6,11-dihydro-5H-dibenzo-[b,e]azepin-11-yl)acetate (4) with methyl bromoacetate in analogy to the synthesis of building block 1 afforded 13.8 g of a pale yellowish oil, which was directly hydrolyzed further with KOH in 5 dioxane/H<sub>2</sub>O (11.2 g); ESI-MS [M+H<sup>+</sup>-tBu] = 326.15.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 360 MHz) diastereomer mixture: δ (ppm): 7.80-7.0 (m, 8H), 4.8-4.6 (m, 2H), 4.55 (m, 1H), 3.6-3.1 (broad m, overlapped by H<sub>2</sub>O, 2H), 3.05 (m, 2H), 1.3/1.15 (s, 9H).

10

[6-(1H-Benzimidazol-2-yl)pyridin-3-yl]methanamine (bistrifluoroacetate) (67)

15 a) Preparation took place in analogy to 13 starting from tert-butyl (6-cyanopyridin-3-yl)methylcarbamate (6.0 g, 25.72 mmol); crystallization of the crude product from methanol afforded 5.15 g; ESI-MS [M+H<sup>+</sup>] = 325.

20 b) 0.55 g of the Boc-protected amine 67a in 10 ml of CH<sub>2</sub>Cl<sub>2</sub> were mixed with 5 ml of TFA and stirred at RT for 2 h. Evaporation of the reaction mixture afforded 0.95 g of a white solid; ESI-MS [M+H<sup>+</sup>] = 225.25.

N<sup>1</sup>-Pyridin-2-ylpropane-1,3-diamine (68)

25

2-Bromopyridine (100 g; 0.633 mol) and 1,3-diaminopropane (234.5 g; 3.16 mol) were refluxed for 7 h. After the reaction was complete, the mixture was evaporated, and distillation of the remaining residue under oil pump vacuum afforded 43 g of the 30 required product; ESI-MS [M+H<sup>+</sup>] = 152.15.

<sup>1</sup>H-NMR (360 MHz, CDCl<sub>3</sub>) δ (ppm): 8.05 (d, 1H), 7.36 (t, 1H), 6.51 (t, 1H), 6.36 (d, 1H), 4.98 (s, 1H), 3.35 (s, 2H), 2.82 (t, 2H), 1.73 (m, 1H), 1.32 (s, 2H).

35

(11E/Z)-11-(3-Methoxy-3-oxopropylidene)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-5-yl acetate (69)

40 a) A suspension of 100 g (448 mmol) of 5H-dibenzo[b,e]azepine-6,11-dione in 2000 ml of toluene was added dropwise to 448 ml of a 1.5 molar vinyl Grignard solution while cooling in ice. The mixture was stirred at RT overnight and then 70 ml of ice-water were added, and precipitated salts were filtered off with suction, dried and 45 concentrated to half the original volume. Filtration with

suction and drying of the resulting precipitate afforded a total of 64.2 g.

- b) A mixture of 39 g of 69a, 3 g of triphenylphosphine, 1 g of PdCl<sub>2</sub> and 40 ml of ethanol was treated with CO (550 to 650 bar) in a 300 ml autoclave at 80 to 100°C for 20 h. The resulting precipitate was filtered off with suction, recrystallized from glacial acetic acid and then stirred with CH<sub>2</sub>Cl<sub>2</sub> (33 g; m.p.: >250°C).

10

11-(3-Methoxy-3-oxopropyl)-6-oxo-6,11-dihydro-5H-dibenzo-[b,e]azepin-5-yl acetate (70)

- Hydrogenation of 69 in analogy to the preparation of 2 afforded 100 mg of methyl 3-[5-(2-tert-butoxy-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]propanoate, which were then reacted with TFA to give the title compound (90 mg); ESI-MS [M+H<sup>+</sup>] = 354.25.

- 20 (10E/Z)-10-(2-Methoxy-2-oxoethylidene)-4-oxo-4H-thieno-[3,4-c][1]benzazepin-5(10H)-yl acetate (71)

- 4H-Thieno[3,4-c][1]benzazepine-4,10(5H)-dione (preparation described in EP 0209022; 0.9 g; 4.33 mmol) was reacted by a standard method with methyl diethyl phosphonoacetate and sodium methanolate as base in 100 ml, and purification of the crude product by chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH 0 to 2 %) and stirring in diethyl ether afforded 1.1 g. Alkylation with tert-butyl bromoacetate in analogy to 2 and subsequent ester cleavage with TFA afforded 85 mg of the title compound; ESI-MS [M+H<sup>+</sup>] = 344.

10-(2-Methoxy-2-oxoethyl)-4-oxo-4H-thieno[3,4-c][1]benzazepin-5(10H)-yl acetate (72)

35

Hydrogenation of 71 in analogy to the preparation of 2 and subsequent TFA cleavage afforded the title compound (45 mg); ESI-MS [M+H<sup>+</sup>] = 346.

- 40 (9E/Z)-9-(2-Methoxy-2-oxoethylidene)-5-oxo-9H-dithieno[3,4-b:3,4-e]azepin-4(5H)-yl acetate (73)

- Synthesis took place in analogy to building block 71 starting from 9H-dithieno[3,4-b:3,4-e]azepine-5,9(4H)-dione (preparation described in EP 0209773). 62 mg of the title compound were isolated; ESI-MS [M+H<sup>+</sup>] = 350.

9-(2-Methoxy-2-oxoethyl)-5-oxo-9H-dithieno[3,4-b:3,4-e]azepin-4(5H)-yl acetate (74)

Hydrogenation of 73 in analogy to the preparation of 2 and subsequent TFA cleavage afforded the title compound (20 mg); ESI-MS  $[M+H]^+$  = 352.

2-{{11-(2-tert-Butoxy-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-5-yl}methyl}-1,3-thiazole-4-carboxylic acid (75)

10

a) Alkylation of 5 g (15.46 mmol) of tert-butyl (6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl acetate (4) with bromoacetonitrile in analogy to 1 afforded 5.5 g of a brownish oil (ESI-MS  $[M+H]^+$  = 363.15), which was reacted directly with  $H_2S$  in pyridine with addition of triethylamine to give a thioamide. The crude product obtained after workup was stirred with n-pentane (7 g).

15

b) Reaction of the thioamide (4 g; 10.1 mmol) with ethyl bromopyruvate in 30 ml with the addition of 0.83 g of  $KHCO_3$  led to ethyl 2-{{11-(2-tert-butoxy-2-hydroxypropyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-5-yl}methyl}-1,3-thiazole-4-carboxylate (4.1 g; ESI-MS  $[M+H]^+$  = 493.15), of which 3 g were hydrolyzed with KOH in dioxane/ $H_2O$  (2 g; ESI-MS  $[M+H]^+$  = 465.15).

25

#### Examples I.B

Examples of the synthesis of compounds of the formula I (B-G-L):

30

#### Example I.B.1

6-Oxo-5-(2-oxo-2-{{2-(2-pyridinylamino)ethyl}amino}ethyl)-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl acetate (15)

35 a) 11-(2-Methoxy-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-5-yl acetate 3 (0.45 g; 1.33 mmol) was dissolved in 25 ml of  $CH_2Cl_2$  and, at  $0^\circ C$ , 1.1 eq. of N'-(dimethylaminopropyl)-N-ethylcarbodiimide (0.28 g) and 1.03 eq. of N-methylmorpholine (0.15 ml) were added. After about 40 min., N-(2-pyridinyl)-1,2-ethanediamine (0.18 g; 1.33 mmol) was added and the mixture was stirred at RT. After the reaction was complete (about 2 h), the mixture was diluted with  $CH_2Cl_2$ , washed with saturated NaCl solution, dried and concentrated. The remaining residue (0.49 g) was purified by chromatography on silica gel ( $CH_2Cl_2/CH_3OH$  3 to 10%).

45

0.36 g; ESI-MS [M+H<sup>+</sup>] = 459.

- 5 b) Methyl [6-oxo-5-(2-oxo-2-[[2-(2-pyridinylamino)ethyl]-amino]ethyl)-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]-acetate (0.34 g; 0.74 mmol) was dissolved in 15 ml of CH<sub>3</sub>OH and 2 ml of H<sub>2</sub>O and, after addition of a total of 2 eq. of KOH (0.085 g), heated to reflux. After the reaction was complete, the mixture was evaporated, and the resulting crude product was purified by MPLC (silica gel: Bischoff Prontoprep 10 60-2540-C18E, 32 μm; eluent: CH<sub>3</sub>CN/H<sub>2</sub>O + 0.1% acetic acid) and then lyophilized.

0.11 g; ESI-MS [M+H<sup>+</sup>] = 445.1;

15

<sup>1</sup>H-NMR (200 MHz; DMSO-d<sub>6</sub>) diastereomer mixture: δ (ppm) 8.3 (m, 1H), 7.95 (m, 1H), 7.65-7.1 (m, 9H), 6.65-6.30 (m, 3H), 4.8-4.2 (m, 4H), 3.55-3.1 (m, 4H), 3.85 (1H).

## 20 Example I.B.2

6-Oxo-5-(2-oxo-2-[4-(2-pyridinyl)-1-piperazinyl]ethyl)-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl acetate (16)

- 25 a) 11-(2-Methoxy-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]-azepin-5-yl acetate 3 (1.2 g; 3.54 mmol) was dissolved in 25 ml of CH<sub>2</sub>Cl<sub>2</sub> and, at 0°C, 1.1 eq. of N'-(dimethylaminopropyl)-N-ethylcarbodiimide (0.8 g) and 1.0 eq. of DIPEA (ethyl-diisopropylamine) (0.45 g) and, after about 2 h, N-(2-pyridinyl)piperazine (0.57 g; 3.54 mmol) were 30 added. The mixture was then stirred at RT. After the reaction was complete (about 2 h), the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed with saturated NaCl solution, dried and concentrated. The remaining residue (2.03 g) was purified by chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH 2 to 8%).

35

0.57 g; ESI-MS [M+H<sup>+</sup>] = 485.25;

- 40 b) Methyl (6-oxo-5-(2-oxo-2-[4-(2-pyridinyl)-1-piperazinyl]-ethyl)-6,11-dihydro-5H-dibenzo-[b,e]azepin-11-yl)acetate (0.485 g; 1.18 mmol) was dissolved in 30 ml of 5:1 dioxane/H<sub>2</sub>O and, after addition of 1.5 eq. of KOH (0.1 g), heated to reflux. After the reaction was complete, the mixture was evaporated, and the resulting crude product was purified by MPLC (silica gel: Bischoff Prontoprep 45 60-2540-C18E, 32 μm; eluent: CH<sub>3</sub>CN/H<sub>2</sub>O + 0.1% acetic acid) and then lyophilized.

0.21 g; ESI-MS  $[M+H]^+$  = 471.15;

<sup>1</sup>H-NMR (200 MHz; DMSO-d<sub>6</sub>) diastereomer mixture:  $\delta$  (ppm)  
 12.2-11.8 (broad, 1H), 8.15 (m, 1H), 7.7-7.05 (m, 9H), 6.85  
 5 (m, 1H), 6.7 (m, 1H), 5.25-4.25 (4H), 3.75-3 (m, overlapped  
 by H<sub>2</sub>O), 2.85 (m, 1H).

Example I.B.3

5-[2-({[6-(1H-Benzimidazol-2-yl)-3-pyridinyl]methyl}amino)-2-  
 10 oxoethyl]-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl acetate  
 (17)

11-(2-Methoxy-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]-  
 azepin-5-yl acetate 3 (0.56 g; 1.66 mmol) was dissolved in 15 ml  
 15 of CH<sub>2</sub>Cl<sub>2</sub> and, at 0°C, 1.2 eq. of  
 N'-(dimethylaminopropyl)-N-ethylcarbodiimide (0.37 g) and 4.4 eq.  
 of DIPEA (0.95 g) were added. After about 50 minutes,  
 [6-(1H-benzimidazol-2-yl)-3-pyridinyl]methanamine x 2TFA (6)  
 (0.94 g; 1.66 mmol) - dissolved in 15 ml of DMF - was added and  
 20 stirred at RT. After the reaction was complete (about 2 h), the  
 mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed with saturated NaCl  
 solution, dried and concentrated. The resulting crude product  
 (1.4 g) was reacted directly without further purification.

25 ESI-MS  $[M+H]^+$  = 546.25.

Methyl {5-[2-({[6-(1H-benzimidazol-2-yl)-3-pyridinyl]methyl}-  
 amino)-2-oxoethyl]-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-  
 11-yl}acetate (1.4 g) was dissolved in 30 ml of 5:1 dioxane/H<sub>2</sub>O  
 30 and, after addition of 2.15 eq. of KOH (0.2 g), heated to reflux.  
 After the reaction was complete (12 h), the mixture was  
 evaporated, and the resulting crude product was purified by MPLC  
 (silica gel: Bischoff Prontoprep 60-2540-C18E, 32  $\mu$ m; eluent:  
 CH<sub>3</sub>CN/H<sub>2</sub>O + 0.1% acetic acid) and then lyophilized.

35

0.45 g; ESI-MS  $[M+H]^+$  = 532.15

<sup>1</sup>H-NMR (200 MHz; DMSO-d<sub>6</sub>) diastereomer mixture:  $\delta$  (ppm) 12.9 (s,  
 1H), 8.95 (m, 1H), 8.70 (m, 1H), 8.30 (m, 1H), 7.85 (m, 1H),  
 40 7.8-7.05 (m 12H), 4.85-4.25 (m, 4H), 3.75-3.0 (m, overlapped by  
 H<sub>2</sub>O), 2.90 (m, 1H).

The following were prepared analogously:

### Example I.B.4

10-Oxo-11-[2-oxo-2-({4-[(2-pyridinylamino)methyl]benzyl}amino)-ethyl]-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl acetate (18)

5 Coupling with N-[4-(aminomethyl)benzyl]-2-pyridinamine (12) and subsequent hydrolysis of the methyl ester afforded 0.3 g;

ESI-MS [M+H<sup>+</sup>] = 521.25;

<sup>1</sup>H-NMR (200 MHz; DMSO-d<sub>6</sub>) diastereomer mixture: δ (ppm) 8.70 (m, 1H), 7.95 (m, 1H), 7.70–6.95 (m, 15H), 6.45 (m, 2H), 4.85–4.2 (m, 8H), 2.8 (m, 1H).

### Example I.B.5

5-(2-{[2-(4,5-Dihydro-1H-imidazol-2-ylamino)ethyl]amino}-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl acetate (19)

Coupling with N<sup>1</sup>-(4,5-dihydro-1*H*-imidazol-2-yl)-1,2-ethanediamine and subsequent hydrolysis of the methyl ester afforded 0.42 g;

20

ESI-MS  $[M+H^+] = 436.1$ ;

### Example I.B.6

25 2-{5-[(11-oxo-6,11-dihydro-5H-dibenzo[b,e]-  
azepin-5-yl)acetyl]amino)methyl}-2-pyridinyl}-4,5-dihydro-1H-  
imidazol-1-ium acetate (20)

## Coupling with

2-[5-(aminomethyl)-2-pyridinyl]-4,5-dihydro-1H-imidazole and  
30 subsequent hydrolysis of the methyl ester afforded 0.3 g as  
acetate;

ESI-MS  $[M+H^+] = 502.15$ ;

35 <sup>1</sup>H-NMR (200 MHz; DMSO-d<sub>6</sub>) diastereomer mixture: δ (ppm) 9.15-8.80 (m, 2H), 8.65 (m, 1H), 8.1-7.05 (m 10H), 4.8-3.75 (m, overlapped by H<sub>2</sub>O), 3.4 (m 2H), 2.80 (m, 2H), 1.85 (s, 3H).

### Example I.B.7

40 6-Oxo-5-[2-oxo-2-({[1-(2-pyridinyl)-4-piperidinyl]methyl}amino)-  
ethyl]-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl acetate (21)

Coupling with [1-(2-pyridinyl)-4-piperidinyl]methanamine and subsequent hydrolysis of the methyl ester afforded 0.4 g;

45



ESI-MS  $[M+H^+]$  = 499.25;

$^1H$ -NMR (200 MHz; DMSO- $d_6$ ) diastereomer mixture:  $\delta$  (ppm) 12.15 (broad), 8.2 (m 1H), 8.15 (m 1H), 7.75-7.05 (m, 9H), 6.85 (m 1H),  
5 6.6 (m, 1H), 4.8-4.2 (m 4-5H), 3.65-2.7 (m, overlapped by  $H_2O$ ),  
1.70 (m 3H), 1.2 (m, 2H).

Example I.B.8

2-([11-(Carboxymethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]-  
10 azepin-5-yl]acetyl)amino)methyl]-1H-benzimidazol-1-ium acetate  
(22)

Coupling with 1H-benzimidazol-2-ylmethanamine and subsequent hydrolysis of the methyl ester afforded 0.48 g as acetate;

15

ESI-MS  $[M+H^+]$  = 455.15;

$^1H$ -NMR (200 MHz; DMSO- $d_6$ ) diastereomer mixture:  $\delta$  (ppm) 12.1 broad, 8.95 (m 1H), 7.75-7.05 (m 12H), 4.85-4.30 (m, 6H), 2.85 (m  
20 1H), 1.95 (s, 3H).

Example I.B.9

2-([11-(Carboxymethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]-  
azepin-5-yl]acetyl)amino)methyl]-3H-imidazo[4,5-b]pyridin-3-ium  
25 acetate (23)

Coupling with 2-(aminomethyl)-3H-imidazo[4,5-b]pyridine and subsequent hydrolysis of the methyl ester afforded 0.24 g as acetate;

30

ESI-MS  $[M+H^+]$  = 456.15;

$^1H$ -NMR (200 MHz; DMSO- $d_6$ ) diastereomer mixture:  $\delta$  (ppm) 9.8/9.25 (broad), 8.25 (m 1H), 7.95 (m 1H), 7.65-6.8 (m 8-9H), 4.75-4.40  
35 (m 4H), 4.0-2.9 (m, overlapped by  $H_2O$ ), 1.80 (s, 3H).

Example I.B.10

6-Oxo-5-(3-oxo-3-([2-(2-pyridinylamino)ethyl]amino)propyl)-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl acetate (24)  
40

Coupling of 3-[11-(2-tert-butoxy-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-5-yl]propanoic acid (6), subsequent cleavage of the tert-butyl ester with TFA and purification by MPLC afforded 40 mg;

45

<sup>1</sup>H-NMR (200 MHz; DMSO-d<sub>6</sub>) diastereomer mixture: δ (ppm) 8.15 (m 1H), 7.95 (m 1H), 7.70–7.15 (m, 11H), 6.65 (broad, 1H), 6.45 (m 2H), 4.70 (m 1H), 4.40 (m 2H), 4.25–2.6 (m, overlapped by H<sub>2</sub>O).

6-Oxo-5-{3-oxo-3-[4-(2-pyridinyl)-1-piperazinyl]propyl}-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl acetate (25)

10

ESI-MS  $[M+H^+] = 485.25;$

Example I.B.12

20 mg were obtained in analogy to Example 10;

25

<sup>1</sup>H-NMR (200 MHz; DMSO-d<sub>6</sub>) diastereomer mixture: δ (ppm) 12.2 (broad), 8.70 (m 1H), 8.10 (m, 1H), 7.80-6.95 (m, 13H), 4.70 (m 1H), 4.60-3.90 (m, 5H), 3.55-2.85 (m, overlapped by H<sub>2</sub>O).

2-{[(1-{[11-(Carboxymethyl)-6-oxo-6,11-dihydro-5H-dibenzo-  
[b,e]azepin-5-yl]acetyl}-4-piperidinyl)methyl]amino}pyridinium  
acetate (28)

35

40 ESI-MS  $[M+H^+] = 499.25$ ;

1H-NMR (200 MHz; DMSO-d6) diastereomer mixture:  $\delta$  (ppm) 8.05 (m, 1H), 7.80-7.15 (m, 9H), 6.70 (m, 1H), 6.55 (m, 2H), 5.35-4.80 (m, 3H), 4.70-4.0 (m, 3H), 3.75-2.80 (m, overlapped by H<sub>2</sub>O), 2.05 (s, 45 3H), 2.80 (m, 3H), 1.25 (m 2H).

Example I.B.15

5-(2-{4-[(Benzylamino)carbonyl]-1-piperazinyl}-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl acetate (29)

- 5 a) 11-(2-Methoxy-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]-azepin-5-yl acetate 3 (2.5 g; 7.37 mmol) was dissolved in 40 ml of CH<sub>2</sub>Cl<sub>2</sub> and "preactivated" - as described above - by adding 1.2 eq. of N'-(dimethylaminopropyl)-N-ethylcarbodiimide (1.15 g) and 1.2 eq. of DIPEA (1.15 g). After 1 h, Boc-piperazine (1.37 g) was added, and the mixture was stirred at 0°C for 1 h and then at RT. For workup, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed with saturated NaCl solution, dried and concentrated. The resulting crude product (3.2 g) was purified by chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH 1 to 3% + 0.1% acetic acid). 1.7 g; ESI-MS [M+H<sup>+</sup>] = 508.2;
- 10 b) 5-{2-[4-(tert-Butoxycarbonyl)-1-piperazinyl]-2-oxoethyl}-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl acetate (1.7 g) was dissolved in 20 ml of CH<sub>2</sub>Cl<sub>2</sub> and, at 0°C, 10 ml of TFA were added. After the reaction was complete, the mixture was concentrated and coevaporated 2x with toluene (1.75 g; ESI-MS [M+H<sup>+</sup>] = 408.15).
- 15 The TFA salt was then dissolved in 30 ml of 1:1 toluene/dioxane and, after addition of 2 eq. of DIPEA (0.4 g) and 1 eq. of benzyl isocyanate (0.2 g), heated to reflux. After the reaction was complete, the mixture was concentrated, taken up in CH<sub>2</sub>Cl<sub>2</sub>, washed with 1N HCl solution and then saturated NaCl solution, dried and evaporated (0.81 g; ESI-MS [M+H<sup>+</sup>] = 541.25). Hydrolysis was effected by dissolving in 25 ml of 2:1 dioxane/H<sub>2</sub>O, adding 1.5 eq. of KOH (0.13 g) and heating to reflux. The mixture was then concentrated, acidified with 2N HCl and extracted 2x with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were then washed with saturated NaCl solution, dried and again concentrated, and the resulting residue was stirred with methyl tert-butyl ether.
- 20 0.36 g; ESI-MS [M+H<sup>+</sup>] = 527.15;
- 25 <sup>1</sup>H-NMR (200 MHz; DMSO-d<sub>6</sub>) diastereomer mixture: δ (ppm) 7.7-7.1 (m, 14H), 5.25-4.1 (4H), 3.7-3.1 (m, overlapped by H<sub>2</sub>O), 2.95 (m, 1H).
- 30
- 35
- 40
- 45

Example I.B.16

5-[2-([5-(1H-Benzimidazol-2-yl)-2-thienyl]methyl)amino]-2-oxoethyl]-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl acetate (30)

5

- a) 11-(2-Methoxy-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo-  
[b,e]azepin-5-yl acetate 3 (4 g; 11.8 mmol) was dissolved in  
30 ml of CH<sub>2</sub>Cl<sub>2</sub> and "preactivated" - as described above - by  
adding 1.15 eq. of  
10 N'-(dimethylaminopropyl)-N-ethylcarbodiimide (2.6 g) and  
1.6 eq. of DIPEA (2.5 g). After 1 h,  
5-(aminomethyl)-3-thiophenecarbonitrile (1.92 g) - dissolved  
in 35 ml of DMF - and a further 1 ml of DIPEA were added, and  
the mixture was stirred at 0°C for 1 h and then at RT. The  
15 usual workup afforded 6.6 g of yellow oil which was purified  
by chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH 1 to 3%).  
4.1 g; ESI-MS [M+H<sup>+</sup>] = 460.15;
- b) Methyl [10-(2-([5-(5-cyano-2-thienyl)methyl]amino)-2-oxoethyl)-  
11-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl]acetate  
20 (0.85 g; 1.85 mmol) was dissolved in 15 ml of pyridine and,  
at 0°C, 1.76 g of triethylamine were added, and H<sub>2</sub>S was passed  
in for 90 minutes. After 1 h at RT, the reaction mixture was  
concentrated, and CH<sub>2</sub>Cl<sub>2</sub> was added and reevaporated 2x (0.9 g  
25 of yellow foam).  
The thioamide was then dissolved in 20 ml of CH<sub>2</sub>Cl<sub>2</sub> and, after  
addition of 5 eq. of CH<sub>3</sub>I (1.3 g), stirred at RT overnight.  
The mixture was evaporated, and the residue was taken up in  
25 ml of CH<sub>3</sub>OH, mixed with 1,2-phenylenediamine (0.197 g) and  
30 stirred at RT for 3 h. Concentration of the mixture afforded  
1.35 g of crude product which was purified by chromatography  
on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH).  
0.46 g; ESI-MS [M+H<sup>+</sup>] = 551.15.
- 35 Hydrolysis of the methyl ester took place in analogy to the  
examples already described in 20 ml of 3:1 dioxane/H<sub>2</sub>O with 80 mg  
of KOH at RT. Workup and purification of the crude product by  
MPLC (silica gel: Bischoff Prontoprep 60-2540-C18E, 32 μm;  
eluent: CH<sub>3</sub>CN/H<sub>2</sub>O + 0.1% acetic acid) afforded 0.22 g of the  
40 required product.  
ESI-MS [M+H<sup>+</sup>] = 537.15;

<sup>1</sup>H-NMR (200 MHz; DMSO-d<sub>6</sub>) diastereomer mixture: δ (ppm) 8.85 (m,  
1H), 7.75-7.2 (m, 14H), 4.85-4.3 (m, 6H), 3.5-3.1 (m, overlapped  
45 by H<sub>2</sub>O), 2.95 (m, 1H).

## Example I.B.17

(5-{2-([4-[Amino(imino)methyl]-2-thienyl)methyl]amino}-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl}acetic acid (31)

5

Methyl-[5-(2-([4-(4-cyano-2-thienyl)methyl]amino)-2-oxoethyl)-6-oxo-6,11-dihydro-5H-di-benzo-[b,e]azepin-11-yl}acetate and the corresponding thioamide were prepared in analogy to Example 16.

Methyl {5-[2-([4-(thiocarbamoyl)-2-thienyl)methyl]amino)-2-oxoethyl]-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl}acetate (2.3 g; 4.66 mmol) in 30 ml of CH<sub>2</sub>Cl<sub>2</sub> was stirred with 5 eq. of CH<sub>3</sub>I (3.3 g) at RT overnight. The mixture was evaporated, and the residue was taken up in 20 ml of CH<sub>3</sub>OH, mixed with 0.27 g of ammonium acetate and again stirred overnight. Concentration of the mixture afforded 1.44 g of the crude product (ESI-MS [M+H]<sup>+</sup> = 477.15).

The methyl ester was taken up in 10 ml of dioxane and, after addition of 15 ml of 2N HCl refluxed for 6 h. The mixture was then evaporated, and the resulting residue was purified by MPLC (silica gel: Bischoff Prontoprep 60-2540-C18E, 32 μm; eluent: CH<sub>3</sub>CN/H<sub>2</sub>O + 0.1% acetic acid). 0.12 g; ESI-MS [M+H]<sup>+</sup> = 463.05;

<sup>1</sup>H-NMR (200 MHz; DMSO-d<sub>6</sub>) diastereomer mixture: δ (ppm) 10.5-9.1 (broad), 9.05/8.8 (m, 1H), 8.35 (m, 1H), 7.7-7.0 (m, 10H), 4.95-4.15 (m, 6H), 3.6-2.90 (m, overlapped by H<sub>2</sub>O), 2.70 (m, 1H).

## Example I.B.18

{5-[2-([4-(1H-Benzimidazol-2-yl)-2-thienyl)methyl]amino)-2-oxoethyl]-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl}acetic acid (32)

Methyl [5-(2-([4-(4-cyano-2-thienyl)methyl]amino)-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo-[b,e]azepin-11-yl}acetate (0.5 g; 1.09 mmol) in 30 ml of CH<sub>3</sub>OH was refluxed with 0.2 ml of sodium methoxide solution (30% in CH<sub>3</sub>OH) for 7 h. Then 0.2 g of 1,2-phenylenediamine bishydrochloride was added, and the mixture was again refluxed for about 8 h. After the reaction was complete, the mixture was concentrated and the remaining residue was purified by chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH 1 to 3%).

0.13 g; ESI-MS [M+H]<sup>+</sup> = 551.15;

Hydrolysis in 15 ml of 3:1 dioxane/H<sub>2</sub>O with 1.5 eq. of KOH (0.02 g) and purification of the crude product by MPLC (silica gel: Bischoff Prontoprep 60-2540-C18E, 32 μm; eluent: CH<sub>3</sub>CN/H<sub>2</sub>O + 0.1% acetic acid).

111

0.03 g; ESI-MS [M+H<sup>+</sup>] = 537.15;

<sup>1</sup>H-NMR (200 MHz; DMSO-d<sub>6</sub>) diastereomer mixture: δ (ppm) 9.0/8.8 (m, 1H), 8.15 (m, 1H), 7.75-7.0 (m, 14H), 4.85-4.20 (m, 6H), 3.75-2.8 (m, overlapped by H<sub>2</sub>O).

Example I.B.19

{5-[2-({[4-(3H-Imidazo[4,5-b]pyridin-2-yl)-2-thienyl]methyl}-amino)-2-oxoethyl]-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl}acetic acid (33)

Analogously by reaction with 2,3-pyridinamine.

32 mg; ESI-MS [M+H<sup>+</sup>] = 538.4;

15

<sup>1</sup>H-NMR (200 MHz; DMSO-d<sub>6</sub>) diastereomer mixture: δ (ppm) 8.95-8.8 (m, 1H), 8.0 (m, 1H), 7.8-7.05 (m, 13H), 4.75-4.1 (m, 6H), 2.95 (m, 1H).

20 Example I.B.20

{5-(2-({[4-(1H-Benzimidazol-2-yl)benzyl]amino}-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl}acetic acid hydrochloride (34)

25 Analogously by reaction with

4-(1H-benzimidazol-2-yl)benzylmethanamine from building block 14.

40 mg; ESI-MS [M+H<sup>+</sup>] = 531.15

<sup>1</sup>H-NMR (400 MHz; DMSO-d<sub>6</sub>) diastereomer mixture: δ (ppm) 8.95-8.8

30 (m, 1H), 8.0 (m, 1H), 7.8-7.05 (m, 13H), 4.75-4.1 (m, 6H), 2.95 (m, 1H).

Example I.B.21

{5-[2-({[4-(1H-benzimidazol-2-yl)-1,3-thiazol-2-yl]methyl}-amino)-2-oxoethyl]-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl}acetic acid (35)

Analogously by reaction with [4-(1H-benzimidazol-2-yl)-1,3-thiazol-2-yl]methanamine.

40 430 mg; ESI-MS [M+H<sup>+</sup>] = 538.15;

<sup>1</sup>H-NMR (360 MHz; DMSO-d<sub>6</sub>) diastereomer mixture: δ (ppm) 9.4/9.3 (m, 1H), 8.9 (m, 1H), 7.8-7.15 (m, 13H), 4.95-4.35 (m, 5H), 3.2 (m, overlapped by H<sub>2</sub>O), 2.95 (m, 1H).

45

## Example I.B.22

(5-(2-(4-(1*H*-Benzimidazol-2-yl)anilino)-2-oxoethyl)-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-11-yl)acetic acid (36)

5 Analogously by reaction with 4-(1*H*-benzimidazol-2-yl)aniline.

100 mg; ESI-MS [ $M+H^+$ ] = 517.15;

<sup>1</sup>H-NMR (360 MHz; DMSO-*d*<sub>6</sub>) diastereomer mixture:  $\delta$  (ppm) 12.75 (broad), 10.6 (m, 1H), 8.2 (m, 2H), 7.9-7.1 (m, 14H), 4.8-4.75 (m, 2H), 4.4 (m, 1H), 3.75-3.0 (m, overlapped by H<sub>2</sub>O), 2.8 (m, 1H).

## Example I.B.23

15 Methyl [10-(2-{[4-(1*H*-benzimidazol-2-yl)benzyl]amino}-2-oxoethyl)-11-oxo-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepin-5-yl]acetate

[5-(2-Methoxy-2-oxoethyl)-11-oxo-5,11-dihydro-10*H*-dibenzo-  
20 [*b,e*][1,4]diazepin-10-yl]acetic acid 37c (0.8 g; 2.35 mmol) was dissolved in 50 ml of DMF and, at 0°C, 1.05 g of HATU and 0.3 g of DIPEA were added, and the mixture was stirred at RT for 30 min. Addition of [4-(1*H*-benzimidazol-2-yl)phenyl]methanamine bistrifluoroacetate from building block 14 (1.06 g; 2.35 mmol) and  
25 0.6 g of DIPEA was followed by stirring at 5°C for 2 h. The mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed with H<sub>2</sub>O, dried and concentrated. Chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH 1 → 8%) afforded 1.3 g of a pale brownish oil (ESI-MS [ $M + H^+$ ] = 546.

30 <sup>1</sup>H-NMR (400 MHz; DMSO-*d*<sub>6</sub>):  $\delta$  (ppm) 8.45 (t, 1H), 8.15 (d, 2H), 7.05-7.7 (m, 16H), 4.75 and 4.65 (each d, 2H), 4.45-4.55 (m, 2H), 3.55 (s, 3H).

## Example I.B.24

35 [10-(2-{[4-(1*H*-Benzimidazol-2-yl)benzyl]amino}-2-oxoethyl)-11-oxo-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepin-5-yl]acetic acid (acetate)

Methyl [10-(2-{[4-(1*H*-benzimidazol-2-yl)benzyl]amino}-  
40 2-oxoethyl)-11-oxo-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepin-5-yl]acetate (1 g; 1.56 mmol) and 0.15 g of KOH were refluxed in 30 ml of 2:1 dioxane/H<sub>2</sub>O for 3 h. Concentration of the mixture and chromatography of the crude product by MPLC (silica gel: Bischoff Prontoprep 60-2540-C<sub>18</sub>E, 32  $\mu$ m; eluent: CH<sub>3</sub>CN/H<sub>2</sub>O + 0.1% acetic  
45 acid) afforded 0.22 g of the required product as acetate; ESI-MS [ $M+H^+$ ] = 532.

<sup>1</sup>H-NMR (400 MHz; DMSO-d<sub>6</sub>): δ (ppm) 12.75 (s br, 1H), 8.40 (t, 1H), 8.15 (d, 2H), 7.15-7.7 (m, 16H), 4.75 and 4.60 (each d, 2H), 4.45-4.55 (m, 2H), 2.1 (s, 3H).

5 Example I.B.25

Methyl [10-(2-{{(2-{{(benzylamino)carbonyl}amino}-1,3-thiazol-4-yl)methyl}amino}-2-oxoethyl)-11-oxo-10,11-dihydro-5H-dibenzo[b,e][1,4]diazepin-5-yl]acetate

- 10 Preparation took place in analogy to I.B.23 by reacting [5-(2-methoxy-2-oxoethyl)-11-oxo-5,11-dihydro-10H-dibenzo[b,e][1,4]diazepin-10-yl]acetic acid 37c with *N*-[4-(aminomethyl)-1,3-thiazol-2-yl]-*N'*-benzylurea (hydrochloride) (38). Chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH 2 → 10%) afforded 0.45 g; ESI-MS [M + 15 H<sup>+</sup>] = 585.25.

Example I.B.26

- [10-(2-{{(2-{{(Benzylamino)carbonyl}amino}-1,3-thiazol-4-yl)-methyl}amino}-2-oxoethyl)-11-oxo-10,11-dihydro-5H-dibenzo-  
20 [b,e][1,4]diazepin-5-yl]acetic acid

Hydrolysis of the methyl ester in analogy to I.B.24 and purification of the crude product by MPLC afforded 0.11 g; ESI-MS [M + H<sup>+</sup>] = 571.25.

25

Example I.B.27

- [10-(2-{{(2-{{Amino(imino)methyl}amino}-1,3-thiazol-5-yl)methyl}-amino}-2-oxoethyl)-11-oxo-10,11-dihydro-5H-dibenzo[b,e][1,4]-  
30 diazepin-5-yl]acetic acid

Reaction in analogy to I.B.23 with [4-(aminomethyl)-1,3-thiazol-2-yl]guanidine (bishydrochloride) (39) afforded 0.09 g; ESI-MS [M + H<sup>+</sup>] = 535.15.

35 Example I.B.28

[5-(2-{{3-(1H-Imidazol-2-ylamino)-3-oxopropyl}amino}-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]acetic acid

- a) 440 mg (1.3 mmol) of 11-(2-methoxy-2-oxoethyl)-6-oxo-  
40 6,11-dihydro-5H-dibenzo[b,e]-azepin-5-yl acetate (3) were dissolved in 15 ml of DMF, and 0.3 ml of DIPEA and 543 mg of HATU were added. After 30 min at room temperature, 3-amino-*N*-(1H-imidazol-2-yl)propanamide 42 (200 mg, 1.3 mmol) dissolved in DMF was slowly added dropwise, and the mixture  
45 was stirred for 6 h. It was taken up in ethyl acetate and water and shaken 3x with H<sub>2</sub>O and 3x with NaHCO<sub>3</sub> solution. the organic phase was dried and concentrated, and the remaining



residue was dissolved in  $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$  19:1 and precipitated with diethyl ether. The precipitate was filtered off with suction, washed and dried (220 mg). ESI-MS  $[\text{M}+\text{H}^+] = 476$ .

- 5 b) I.B.28a was dissolved in 5 ml of THF, and a solution of 45 mg of LiOH (1.89 mmol) in aqueous solution was added. The mixture was stirred at RT until the reaction was complete and was then acidified with 10% citric acid and concentrated. A white precipitate separated out and was filtered off with suction, washed 4x with  $\text{H}_2\text{O}$  and dried in vacuo (120 mg); ESI-MS  $[\text{M}+\text{H}^+] = 462$ .

#### Example I.B.29

(5-{2-[4-({[(Benzylamino)carbonyl]amino)methyl]piperidin-11-yl]-2-oxoethyl}-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl)acetic acid

- a) Coupling of 11-(2-Methoxy-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-5-yl] acetate (3) with N-benzyl-N'-(piperidin-4-ylmethyl)carbamate (THL 31, 47, 1990, 6903) in analogy to Example I.B.1 and subsequent purification afforded 1.65 g, which were then hydrogenated under standard conditions with 5% Pd on active carbon in 20 ml of  $\text{CH}_3\text{COH}$  and addition of 1.35 ml of 2 N HCl (1.04 g).
- b) Reaction of the free amine (0.21 g) with 0.06 g of benzyl isocyanate and 0.046 g of N-methylmorpholine in 15 ml of  $\text{CH}_2\text{Cl}_2$  under reflux, washing of the mixture with aqueous 1 N HCl and saturated NaCl solution and concentration afforded 0.17 g of a yellowish oil; ESI-MS  $[\text{M}+\text{H}^+] = 569.25$ .
- c) Hydrolysis of the methyl ester under standard conditions in analogy to I.B.1 and the usual workup afforded 0.16 g as a white solid foam; ESI-MS  $[\text{M}+\text{H}^+] = 555.25$ .

The following were prepared in analogy to Example I.B.10:

#### Example I.B.30

6-Oxo-5-(3-oxo-3-{{[(1-pyridin-2-yl)piperidin-4-yl]methyl}-amino}propyl)-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl acetate

- Coupling of 3-[11-(2-tert-butoxy-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-5-yl]propanoic acid 6 with [1-(2-pyridinyl)-4-piperidinyl]methanamine, subsequent cleavage of the tert-butyl ester with TFA and purification by MPLC afforded 106 mg; ESI-MS  $[\text{M}+\text{H}^+] = 513.25$ .

## Example I.B.31

5-{3-([1-[(Benzylamino)carbonyl]piperidin-4-yl)methyl)-amino]-3-oxopropyl}-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl acetate

5

Coupling with 4-(aminomethyl)-N-benzylpiperidine-1-carboxamide (43), cleavage of the tert-butyl ester with TFA and purification by MPLC afforded 0.46 g; ESI-MS [M+H<sup>+</sup>] = 569.25.

## 10 Example I.B.32

5-[3-([5-(1H-Benzimidazol-2-yl)thien-2-yl)methyl]amino)-3-oxopropyl]-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl acetate

15 Coupling with [5-(1H-benzimidazol-2-yl)thien-2-yl]methanamine (45), cleavage of the tert-butyl ester with TFA and purification by MPLC afforded 70 mg; ESI-MS [M+H<sup>+</sup>] = 551.15.

## Example I.B.33

20 5-[3-([4-(1H-Benzimidazol-2-yl)thien-2-yl)methyl]amino)-3-oxopropyl]-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl acetate

Coupling with [4-(1H-benzimidazol-2-yl)thien-2-yl]methanamine (44), cleavage of the tert-butyl ester with TFA and purification

25 by MPLC afforded 20 mg; ESI-MS [M+H<sup>+</sup>] = 551.15.

The following were prepared in analogy to Example I.B.1:

## Example I.B.34

30 5-{2-([1-[(Benzylamino)carbonyl]piperidin-4-yl)methyl]amino)-2-oxoethyl}-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl acetate

Coupling of 11-(2-methoxy-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-5-yl acetate (3) with 4-(aminomethyl)-N-benzylpiperidine-1-carboxamide (43), ester cleavage and subsequent purification resulted in 0.42 g as a solid foam; ESI-MS [M+H<sup>+</sup>] = 555.25.

## 40 Example I.B.35

5-(2-[4-([1-[(Benzylamino)carbonyl]amino)methyl]benzyl]amino)-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl acetate

45

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Coupling of 3 with *N*-[4-(aminomethyl)benzyl]-*N'*-benzylurea (40), ester cleavage and subsequent purification resulted in 0.62 g as a solid foam.

5 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 400 MHz) diastereomer mixture: δ (ppm) 7.70-7.10 (m, 13H), 6.65-6.5 (m, 2H), 4.75-4.65 (m, 2H), 4.5-4.2 (m, 5H), 3.55, 3.25 (each dd, 1H), 2.0-1.85 (m, 2H).

## Example I.B.36

10 6-Oxo-5-{2-oxo-2-[4-(pyridin-2-ylamino)piperidin-1-yl]ethyl}-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-11-yl acetate

Coupling of 3 with 2-(piperidin-4-ylamino)pyridine (46), ester cleavage and subsequent purification resulted in 0.3 g as a solid  
15 foam; ESI-MS [M+H<sup>+</sup>] = 485.15.

## Example I.B.37

5-(2-{[4-(1*H*-Benzimidazol-2-ylamino)benzyl]amino}-2-oxoethyl)-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-11-yl acetate

20

Coupling of 11-(2-*tert*-butoxy-2-oxoethyl)-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-5-yl acetate (66) with *N*-[4-(aminomethyl)-phenyl]-1*H*-benzimidazol-2-amine (hydrochloride) (47) using HATU as coupling reagent, ester cleavage with TFA and purification of  
25 the crude product by MPLC afforded 0.4 g; ESI-MS [M+H<sup>+</sup>] = 546.25.

## Example I.B.38

Methyl-[5-(2-{[4-(1*H*-benzimidazol-2-ylamino)benzyl]amino}-2-oxoethyl)-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-11-yl  
30 acetate

5-(2-{[4-(1*H*-Benzimidazol-2-ylamino)benzyl]amino}-2-oxoethyl)-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-11-yl acetate I.B.37 (0.9 g; 0.16 mmol) was suspended in 5 ml of CH<sub>3</sub>OH and, after  
35 dropwise addition of 0.02 ml of SOCl<sub>2</sub>, stirred at RT for 48 h. For workup, the reaction mixture was evaporated and stirred with *n*-pentane (40 mg); ESI-MS [M+H<sup>+</sup>] = 560.25.

## Example I.B.39

40 5-(2-{[5-(1*H*-Benzimidazol-2-ylamino)pentyl]amino}-2-oxoethyl)-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-11-yl acetate

Coupling of 3 with N<sup>1</sup>-(1*H*-benzimidazol-2-yl)pentane-1,5-diamine (hydrochloride) (48) using HATU as coupling reagent, cleavage of  
45 the methyl ester in analogy to Example I.B.1 and filtration of

the resulting crude product through a Chromabond C<sub>18</sub> cartridge afforded 0.24 g; ESI-MS [M+H<sup>+</sup>] = 525.6.

Example I.B.40

- 5 5-(2-{[4-(1*H*-Benzimidazol-2-ylamino)butyl]amino}-2-oxoethyl)-  
6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-11-yl acetate

Coupling of 11-(2-*tert*-butoxy-2-oxoethyl)-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-5-yl acetate (66) with N<sup>1</sup>-(1*H*-benzimidazol-2-yl)butane-1,4-diamine (trifluoroacetate) (49) using HATU as coupling reagent, cleavage of the *tert*-butyl ester and purification of the resulting crude product by RP-MPLC afforded 94 mg; ESI-MS [M+H<sup>+</sup>] = 512.25.

15 Example I.B.41

- 5-{2-{[3-{[(Benzylamino)carbonyl]amino}benzyl]amino}-2-oxoethyl)-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-11-yl acetate

Coupling of 11-(2-*tert*-butoxy-2-oxoethyl)-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-5-yl acetate (66) with (3-{[(benzylamino)-carbonyl]amino}phenyl)methanamine (hydrochloride) (41), TFA cleavage and stirring of the resulting crude product with methyl *tert*-butyl ether/CH<sub>3</sub>OH 19:1 afforded 0.61 g of slightly brownish solids; ESI-MS [M+H<sup>+</sup>] = 563.25.

25

Example I.B.42

- 5-(2-{4-[(1*H*-Benzimidazol-2-ylamino)methyl]piperidin-1-yl}-2-oxoethyl)-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-11-yl acetate

30

Coupling of 11-(2-*tert*-butoxy-2-oxoethyl)-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-5-yl acetate (66) with *N*-(piperidin-4-ylmethyl)-1*H*-benzimidazol-2-amine (trifluoroacetate) (50), TFA cleavage and chromatography by RP-MPLC afforded 60 mg; ESI-MS [M+H<sup>+</sup>] = 538.25.

35

Example I.B.43

- 6-Oxo-5-[2-oxo-2-({[2-(pyridin-2-ylamino)-1,3-thiazol-4-yl]-methyl]amino)ethyl]-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-11-yl acetate

40

Coupling of 11-(2-*tert*-butoxy-2-oxoethyl)-6-oxo-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-5-yl acetate (66) with *N*-[4-(aminomethyl)-1,3-thiazol-2-yl]pyridin-2-amine (bishydrochloride) (51), TFA cleavage and chromatography by RP-MPLC afforded 65 mg; ESI-MS [M+H<sup>+</sup>] = 514.15.

45

## Example I.B.44

6-Oxo-5-[2-oxo-2-({[2-(pyridin-2-ylamino)-1,3-thiazol-5-yl]-methyl}amino)ethyl]-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl acetate

5

Coupling of 11-(2-tert-butoxy-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-5-yl acetate (66) with N-[5-(aminomethyl)-1,3-thiazol-2-yl]pyridin-2-amine (bishydrochloride) (52), TFA cleavage and chromatography by RP-MPLC afforded 170 mg; ESI-MS

10 [M+H<sup>+</sup>] = 514.15.

## Example I.B.45

5-(2-({[2-({[Amino(imino)methyl]amino}-1,3-thiazol-4-yl)methyl]-amino}-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl acetate (trifluoroacetate)

15

Coupling of 11-(2-tert-butoxy-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-5-yl acetate (66) with [4-(aminomethyl)-1,3-thiazol-2-yl]guanidine (bishydrochloride) (39), TFA cleavage and chromatography by RP-MPLC afforded 25 mg; ESI-MS [M+H<sup>+</sup>] = 479.15.

20

## Example I.B.46

5-(2-({[2-({[Amino(imino)methyl]amino}-1,3-thiazol-5-yl)-methyl]amino}-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl acetate

25

Coupling of 11-(2-tert-butoxy-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-5-yl acetate (66) with N-[5-(aminomethyl)-1,3-thiazol-2-yl]guanidine (dihydrochloride) (53) and TFA cleavage afforded 70 mg; ESI-MS [M+H<sup>+</sup>] = 479.15.

30

## Example I.B.47

5-[2-({2-[4-(1H-Benzimidazol-2-yl)phenyl]ethyl}amino)-2-oxoethyl]-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl acetate

35

Coupling of 11-(2-tert-butoxy-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-5-yl acetate (66) with 2-[4-(1H-benzimidazol-2-yl)phenyl]ethanamine from building block 54 and TFA cleavage afforded 35 mg; ESI-MS [M+H<sup>+</sup>] = 545.25.

40

## Example I.B.48

6-Oxo-5-{2-oxo-2-[(4-[(pyridin-2-ylamino)methyl]thien-2-yl)-methyl]amino}ethyl]-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl acetate

45

Coupling of 11-(2-tert-butoxy-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-5-yl acetate (66) with N-[[5-(aminomethyl)-thien-3-yl]methyl]pyridin-2-amine (trifluoroacetate) (55) and TFA cleavage afforded 170 mg; ESI-MS [M+H<sup>+</sup>] = 527.25.

5

Example I.B.49

5-(2-{Methyl-[2-(pyridin-2-ylamino)ethyl]amino}-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl acetate

10 Coupling of 11-(2-tert-butoxy-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-5-yl acetate (66) with N<sup>1</sup>-methyl-N<sup>2</sup>-pyridin-2-ylethane-1,2-diamine (acetate) (56), TFA cleavage and RP-MPLC afforded 130 mg; ESI-MS [M+H<sup>+</sup>] = 459.25.

15 Example I.B.50

6-Oxo-5-(2-oxo-2-[[4-(2-pyridinylamino)benzyl]amino]ethyl)-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl acetate

Coupling of 3 with N-[4-(aminomethyl)phenyl]-2-pyridinamine (57),  
20 cleavage of the methyl ester in analogy to Example I.B.1 and filtration of the resulting crude product through a Chromabond C<sub>18</sub> cartridge afforded 3 mg; ESI-MS [M+K<sup>+</sup>] = 545.3, [M+H<sup>+</sup>] = 507.2, 326.0, 254.1.

25 Example I.B.51

Methyl (5-{2-[(4-[(benzylamino)carbonyl]amino)benzyl]amino}-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl)-acetate

30 Coupling of 3 with N-[4-(aminomethyl)phenyl]-N'-benzylurea (trifluoroacetate) (58) and purification of the crude product by chromatography on silica gel afforded 550 mg; ESI-MS [M+K<sup>+</sup>] = 615.2, [M+H<sup>+</sup>]: 577.35.

35 Example I.B.52

(5-{2-[(4-[(Benzylamino)carbonyl]amino)benzyl]amino}-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl)acetic acid

Hydrolysis of the methyl ester from I.B.51 in analogy to I.B.1  
40 and purification of the crude product by RP-MPLC afforded 174 mg; ESI-MS [M+K<sup>+</sup>] = 601.25, [M+H<sup>+</sup>]: 563.35.

Example I.B.53

45 {4-[(11-(Carboxymethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-5-yl)acetyl]amino)methyl}anilino}(imino)methanamine (trifluoroacetate)

## 120

Coupling of 11-(2-tert-butoxy-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-5-yl acetate (66) with [4-(aminomethyl)-phenyl]guanidine (bishydrochloride) (59), TFA cleavage and purification of the crude product by RP-MPLC afforded 7.8 mg;  
 5 ESI-MS  $[M+K^+] = 510.1$ ,  $[M+H^+] = 472.15$ .

## Example I.B.54

[5-(2-{[4-(5-Chloro-1H-benzimidazol-2-yl)benzyl]amino}-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]acetic acid

10

Coupling of 3 with [4-(5-chloro-1H-benzimidazol-2-yl)phenyl]-methanamine (trifluoroacetate) (60) and cleavage of the methyl ester in analogy to I.B.1 afforded 25 mg; ESI-MS  $[M+H^+]$ : 565.25.

## 15 Example I.B.55

[5-(2-{[4-(5,6-Dimethyl-1H-benzimidazol-2-yl)benzyl]amino}-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]acetic acid

20 Coupling of 3 with [4-(5,6-dimethyl-1H-benzimidazol-2-yl)phenyl]-methanamine (trifluoroacetate) (61) and cleavage of the methyl ester in analogy to Example I.B.1 afforded 100 mg; ESI-MS  $[M+H^+]$ : 559.25.

## 25 Example I.B.56

[6-Oxo-5-(2-oxo-2-{[3-(2-pyridinylamino)propyl]amino}ethyl)-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]acetic acid

Coupling of 3 with  $N^1$ -(2-pyridinyl)-1,3-propanediamine (68) and  
 30 cleavage of the methyl ester in analogy to Example I.B. afforded 8 mg; ESI-MS  $[M+H^+]$ : 459.25.

## Example I.B.57

Methyl [6-oxo-5-(2-oxo-2-{4-[2-(2-pyridinylamino)ethyl]-1-piperidinyl}ethyl)-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]-acetate

40

Coupling of 3 with  $N$ -[2-(4-piperidinyl)ethyl]-2-pyridinamine (trifluoroacetate) (62) afforded 140 mg; ESI-MS  $[M+H^+]$ : 527.25.

## Example I.B.58

[6-Oxo-5-(2-oxo-2-{4-[2-(2-pyridinylamino)ethyl]-1-piperidinyl}ethyl)-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]acetic acid

45 Hydrolysis of the methyl ester from Example I.B.57 with LiOH in ethanol/H<sub>2</sub>O afforded 90 mg; ESI-MS  $[M+K^+] = 551.2$ ,  $[M+H^+]$ : 513.25.

## Example I.B.59

Methyl [6-oxo-5-(2-oxo-2-{3-[2-(2-pyridinylamino)ethyl]-1-pyrrolidinyl}ethyl)-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]-acetate

5

Coupling of 3 with N-[2-(3-pyrrolidinyl)ethyl]-2-pyridinamine (trifluoroacetate) (63) afforded 150 mg; ESI-MS  $[M+K^+]$  = 551.2,  $[M+H^+]$ : 513.25.

## 10 Example I.B.60

[6-Oxo-5-(2-oxo-2-{3-[2-(2-pyridinylamino)ethyl]-1-pyrrolidinyl}-ethyl)-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]acetic acid

Hydrolysis of the methyl ester from Example I.B.59 afforded

15 150 mg; ESI-MS  $[M+K^+]$  = 537.2,  $[M+H^+]$ : 499.25.

## Example I.B.61

{6-Oxo-5-[2-oxo-2-({4-[(3-phenylpropanoyl)amino]benzyl}amino)-ethyl]-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl}acetic acid

20

Coupling of 3 with {4-[(3-phenylpropanoyl)amino]phenyl}-methanamine (hydrochloride) (64) and cleavage of the methyl ester in analogy to Example I.B.1 afforded 100 mg; ESI-MS  $[M+K^+]$  = 600.2,  $[M+H^+]$  = 562.2.

25

## Example I.B.62

(5-{2-[(4-[(Benzyloxy)carbonyl]amino)benzyl]amino}-2-oxo-ethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl)acetic acid

30

Coupling of 11-(2-tert-butoxy-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-5-yl acetate (66) with (4-[(benzyloxy)-carbonyl]amino)phenylmethanamine (hydrochloride) (65) and TFA cleavage afforded 72 mg; ESI-MS  $[M+K^+]$  = 602.2,  $[M+H^+]$ : 564.2, 308.0, 102.2.

35

## Example I.B.63

(5-{2-[(5-[Amino(imino)methyl]-2-thienyl)methyl]amino}-2-oxo-ethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl)acetic acid (acetate)

40

a) Coupling of 3 with 5-(aminomethyl)thiophene-2-carbonitrile afforded 1.35 g of a yellowish oil (ESI-MS  $[M+H^+]$ : 460.15). 1.25 g of this amide in 15 ml of ethanol were mixed with 3 eq. of DIPEA and 2.5 eq. of hydroxylammonium chloride and stirred firstly at RT then at 70°C for 7 h. After addition of a further 1 eq. each of DIPEA and hydroxylammonium chloride, the mixture was stirred at 50°C for 4 h. The reaction mixture

45



was then concentrated, diluted with methyl tert-butyl ether and washed with water. The precipitate formed thereby was filtered off with suction, taken up in  $\text{CH}_2\text{Cl}_2$ , again washed with  $\text{H}_2\text{O}$  and evaporated. Stirring of the remaining residue with ethanol/petroleum ether afforded 1 g of a white amorphous solid.

- b) Methyl (5-{2-[(5-[(hydroxyamino)(imino)methyl]-3-thienyl)-methyl]amino}-2-oxoethyl}-6-oxo-6,11-dihydro-5H-dibenzo[b,e]-azepin-11-yl)acetate from I.B.63a was introduced into 10 ml of glacial acetic acid and, after addition of 0.69 g of Zn dust, stirred at RT overnight. The reaction mixture was then filtered through Celite and evaporated to dryness (1.3 g); ESI-MS [M+H<sup>+</sup>]: 477.15.

- 15 c) Methyl ester I.B.63b (0.54 g) was mixed with 50 ml of 2 N HCl and refluxed for 4 h. The mixture was then evaporated and the resulting crude product was purified by RP-MPLC (60 mg); ESI-MS  $[M+H]^+$  = 463.18.

Example I.B.64

[5-(5-((Benzylamino)carbonyl)amino)pentyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]acetic acid

- 25 a) 3 g (10.13 mmol) of methyl (6-oxo-5,6-dihydro-11H-dibenzo-  
[b,e]azepin-11-yl)acetate 4a in 100 ml of DMF were mixed with  
1.12 g of potassium tert-butoxide and stirred at RT for  
30 min. Then 2.95 g of 2-(5-bromopentyl)-1H-isoinidole-  
1,3(2H)-dione were added and the mixture was stirred for  
30 14 h. After the reaction was complete, the mixture was poured  
into ice-water and extracted with ethyl acetate, and the  
organic phase was washed 5x with saturated NaCl solution and  
dried. The crude product obtained after evaporation was  
purified by chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>) (3.5 g).

- 35 b) Hydrolysis with hydrazine hydrate and the usual workup  
afforded the free amine, which was likewise prepared by  
chromatography on silica gel ( $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$  0 to 10%).  
Subsequent reaction with benzyl isocyanate in 55 ml of  
40 toluene/DMF 10:1 and the usual workup afforded 260 mg;  
ESI-MS  $[\text{M}+\text{H}^+] = 500.25$ .
- c) Hydrolysis of the methyl ester under standard conditions  
afforded 10 g of the title compound; ESI-MS  $[\text{M}+\text{K}^+] = 524.3$ ,  
45  $[\text{M}+\text{H}^+] = 486.2, 243.6$ .

## Example I.B.65

Methyl (5-{2-[(4-aminobenzyl)oxy]ethyl}-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl)acetate (hydrochloride)

- 5 a) Methyl (6-oxo-5,6-dihydro-11H-dibenzo[b,e]azepin-11-yl)-acetate 4a (10 g; 35.55 mmol) - dissolved in 200 ml of THF - was slowly added dropwise to 36 mmol of lithium diisopropylamide in 200 ml of THF at 0°C and then stirred at 0°C for 1 h. Subsequently about 100 ml of ethylene oxide were  
10 added, and the reaction mixture was stored at about 10°C overnight. The next day, a further approx. 50 ml of ethylene oxide were added, and the mixture was stirred under autogenous pressure at RT for 48 h. For workup, the mixture was poured into saturated NH<sub>4</sub>Cl solution and extracted with  
15 ethyl acetate and the organic phase was washed with 1 NHCl and then with H<sub>2</sub>O. The crude product obtained after drying and concentration was purified by chromatography on silica gel (n-heptane/ethyl acetate 0 to 30%) (4 g); ESI-MS [M+H<sup>+</sup>] = 326.
- 20 b) A solution of the alcohol I.B.65a (3.2 g; 9.84 mmol) in 50 ml of DMF was added dropwise to a suspension of 0.4 g of NaOH (60%; oil removed with n-pentane) in 100 ml of DMF at 0°C, and the mixture was stirred for about 1 h for complete  
25 formation of the anion. Then 9.5 g of 4-nitrobenzyl bromide - dissolved in 50 ml of DMF - were added, and the mixture was stirred at RT for 48 h. For workup, the mixture was poured into saturated NH<sub>4</sub>Cl solution and extracted with ethyl acetate, and the organic phase was washed 5x with saturated  
30 NaCl solution. The crude product obtained after drying and concentration was purified by chromatography on silica gel (n-heptane/ethyl acetate 0 to 30%) (0.8 g).
- c) Reduction of the nitro compound I.B.65b (0.65 g; 1.41 mmol) with H<sub>2</sub> and 10% Pd on active carbon in 100 ml of CH<sub>3</sub>OH  
35 afforded after the workup 650 mg of the title compound; ESI-MS [M+K<sup>+</sup>] = 469.1, [M+Na<sup>+</sup>] = 453.15, [M+H<sup>+</sup>] = 431.25, 236.6, 216.15.

## 40 Example I.B.66

Methyl (5-{2-[(4-{[(benzylamino)carbonyl]amino}benzyl)oxy]ethyl}-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl)acetate

- 0.65 g (1.51 mmol) of the methyl ester I.B.65 were converted with  
45 0.23 g of benzyl isocyanate and 0.17 g of triethylamine in 100 ml of CH<sub>2</sub>Cl<sub>2</sub> into the corresponding benzylurea (purification of the crude product by chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/ethanol)).

Hydrolysis of the ester in analogy to I.B.1 afforded 22 mg of the title compound; ESI-MS  $[M+K^+] = 588.3$ ,  $[M+H^+] = 550.25$ .

Example I.B.67

5 Methyl {5-[4-(4-[(benzylamino)carbonylamino]phenyl)butyl]-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl}acetate

- a) A solution of methyl (6-oxo-5,6-dihydro-11H-dibenzo[b,e]-azepin-11-yl)acetate 4a (0.2 g; 0.72 mmol) in 10 ml of DMF was added dropwise to a suspension of 0.3 g of NaH (60%; oil removed with n-pentane) in 30 ml of DMF at 0°C, and the mixture was then stirred for 1 h for complete formation of the anion. The mixture was subsequently heated to 75°C, and a solution of 4-(4-nitrophenyl)butyl methanesulfonate (0.2 g) in DMF was added. The mixture was stirred at 75°C for 3 h and, for workup, then poured into saturated  $NH_4Cl$  solution and extracted with ethyl acetate, and the organic phase was washed 4x with saturated NaCl solution and concentrated. Alkaline extraction of the crude product obtained in this way afforded 130 mg of methyl {5-[4-(4-nitrophenyl)-butyl]-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl}-acetate; ESI-MS  $[M+H^+] = 445$ .
- b) Reduction of the nitro compound in analogy to I.B.65 afforded the corresponding amine (56 mg; ESI-MS  $[M+H^+] = 415$ ), which was then converted in analogy to I.B.66 with 0.02 g of benzyl isocyanate and 0.015 g of triethylamine into the benzylurea. Purification of the crude product by chromatography on silica gel afforded 5 mg; ESI-MS  $[M+K^+] = 586.2$ ,  $[M+H^+]$ : 548.3, 274.6.

Example I.B.68

N-{4-[(5-(carboxymethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]-azepin-11-yl)acetyl]amino)methyl}phenyl}-1H-benzimidazol-2-amine (hydrochloride)

- a) 0.5 g (1.26 mmol) of methyl [5-(2-tert-butoxy-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]acetate (2) was hydrolyzed by the standard method with LiOH in ethanol/ $H_2O$  to give [5-(2-tert-butoxy-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]acetic acid. Coupling of the acid with N-[4-(aminomethyl)phenyl]-1H-benzimidazol-2-amine (hydrochloride) (47) using HATU as coupling reagent and chromatography of the resulting crude product on silica gel ( $CH_2/Cl_2/CH_3OH$  0 to 2%) afforded 170 mg of tert-butyl-[11-(2-{[4-(1H-benzimidazol-2-ylamino)benzyl]-

amino}-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-5-yl]acetate; ESI-MS [M+H<sup>+</sup>]: 602.

- 5 b) TFA cleavage, dissolving of the crude product in CH<sub>2</sub>Cl<sub>2</sub> and conversion into the corresponding hydrochloride (HCl in diethyl ether; saturated at 0°C) afforded 25 mg of the title compound; ESI-MS [M+H<sup>+</sup>]: 546.2.

The following were prepared analogously:

10

Example I.B.69

[5-(2-([3-(4-Methyl-1H-imidazol-1-yl)propyl]amino)-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]acetic acid

- 15 2 mg; ESI-MS [M+H<sup>+</sup>] = 447.

Example I.B.70

[5-(2-([3-(4-Methyl-1-piperazinyl)propyl]amino)-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]acetic acid

20

- 4 mg; ESI-MS [M+H<sup>+</sup>] = 465.

Example I.B.71

(6-Oxo-5-{2-oxo-2-[(3-pyridinylmethyl)amino]ethyl}-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]acetic acid

25

- 3 mg; ESI-MS [M+H<sup>+</sup>] = 416.

Example I.B.72

[5-(2-([3-(1H-Imidazol-1-yl)propyl]amino)-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]acetic acid

30

- 3 mg; ESI-MS [M+H<sup>+</sup>] = 433.

35 Example I.B.73

[5-(2-([1-Methyl-2-(4-morpholinyl)ethyl]amino)-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]acetic acid

- 3 mg; ESI-MS [M+H<sup>+</sup>] = 452.

40

Example I.B.74

[5-(2-([1-Ethyl-2-pyrrolidinyl)methyl]amino)-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]acetic acid

- 45 2 mg; ESI-MS [M+H<sup>+</sup>] = 436.

Example I.B.75

(6-Oxo-5-{2-oxo-2-[4-(4-pyridinylmethyl)-1-piperazinyl]ethyl}-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl)acetic acid

4 mg; ESI-MS [M+H<sup>+</sup>] = 485.

5

Example I.B.76

[6-Oxo-5-(2-oxo-2-{4-[2-(1-pyrrolidinyl)ethyl]-1-piperazinyl}-ethyl)-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]acetic acid

10 2 mg; ESI-MS [M+H<sup>+</sup>] = 491.

Example I.B.77

[5-(2-{4-[2-(Diethylamino)ethyl]-1-piperazinyl}-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]acetic acid

15

2 mg; ESI-MS [M+H<sup>+</sup>] = 493.

Example I.B.78

[5-(2-{4-[2-(4-Morpholinyl)ethyl]-1-piperazinyl}-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]acetic acid

20

4 mg; ESI-MS [M+H<sup>+</sup>] = 507.

Example I.B.79

(6-Oxo-5-{2-oxo-2-[4-(2-pyrimidinyl)-1-piperazinyl]ethyl}-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl)acetic acid

25

3 mg; ESI-MS [M+H<sup>+</sup>] = 472.

30 Example I.B.80

(6-Oxo-5-{2-oxo-2-[(2-pyridinylmethyl)amino]ethyl}-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl)acetic acid

2 mg; ESI-MS [M+H<sup>+</sup>] = 416.

35

Example I.B.81

[5-(2-{[2-(4-Morpholinyl)ethyl]amino}-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]acetic acid

40 3 mg; ESI-MS [M+H<sup>+</sup>] = 438.

Example I.B.82

[5-(2-{[3-(Dibutylamino)propyl]amino}-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]acetic acid

45

1 mg; ESI-MS [M+H<sup>+</sup>] = 494.

## Example I.B.83

(6-Oxo-5-{2-oxo-2-[4-(4-pyridinyl)-1-piperazinyl]ethyl}-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl)acetic acid

5 2 mg; ESI-MS  $[M+H^+]$  = 471.

## Example I.B.84

[5-(2-{4-[3-(4-Morpholinyl)propyl]-1-piperazinyl}-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]acetic acid

10

3 mg; ESI-MS  $[M+H^+]$  = 521.

## Example I.B.85

[5-(2-{[3-(2-Methyl-1H-imidazol-1-yl)propyl]amino}-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]acetic acid

15

1 mg; ESI-MS  $[M+H^+]$  = 447.

## Example I.B.86

(6-Oxo-5-{2-oxo-2-[(4-pyridinylmethyl)amino]ethyl}-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl)acetic acid

20

1 mg; ESI-MS  $[M+H^+]$  = 416.

## 25 Example I.B.87

(5-{2-[(1-Methyl-4-piperidinyl)amino]-2-oxoethyl}-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl)acetic acid

2 mg; ESI-MS  $[M+H^+]$  = 422.

30

## Example I.B.88

[6-Oxo-5-(2-oxo-2-{[2-(1-piperidinyl)ethyl]amino}ethyl)-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]acetic acid

35 1 mg; ESI-MS  $[M+H^+]$  = 436.

## Example I.B.89

[6-Oxo-5-(2-oxo-2-{4-[3-(1-pyrrolidinyl)propyl]-1-piperazinyl}-ethyl)-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]acetic acid

40

1 mg; ESI-MS  $[M+H^+]$  = 505.

## Example I.B.90

[5-(2-{4-[2-(Dimethylamino)ethyl]-1-piperazinyl}-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]acetic acid

45

128

2 mg; ESI-MS  $[M+H^+] = 465$ ,

Example I.B.91

[5-(2-{4-[3-(Dimethylamino)propyl]-1-piperazinyl}-2-oxoethyl)-  
5 6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]acetic acid

1 mg; ESI-MS  $[M+H^+] = 479$ .

Example I.B.92

10 [5-(2-{4-[2-(Dipropylamino)ethyl]-1-piperazinyl}-2-oxoethyl)-  
6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]acetic acid

1 mg; ESI-MS  $[M+H^+] = 521$ .

15 Example I.B.93

[6-Oxo-5-(2-oxo-2-{4-[2-(1-piperidinyl)ethyl]-1-piperazinyl}-  
ethyl)-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]acetic acid

2 mg; ESI-MS  $[M+H^+] = 505$ .

20

Example I.B.94

[5-(2-{4-[3-(Dipropylamino)propyl]-1-piperazinyl}-2-oxoethyl)-  
6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]acetic acid

25 2 mg; ESI-MS  $[M+H^+] = 535$ .

Example I.B.95

[5-(2-{4-(Dibutylamino)butyl]amino}-2-oxoethyl)-6-oxo-6,11-  
dihydro-5H-dibenzo[b,e]azepin-11-yl]acetic acid

30

2 mg; ESI-MS  $[M+H^+] = 508$ .

Example I.B.96

[6-Oxo-5-(2-oxo-2-{4-[2-oxo-2-(1-pyrrolidinyl)ethyl]-1-piperaziny  
35 l)ethyl)-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]acetic acid

3 mg; ESI-MS  $[M+H^+] = 505$ .

Example I.B.97

40 [5-(2-{3-(Diethylamino)propyl]amino}-2-oxoethyl)-6-oxo-6,11-dihy  
dro-5H-dibenzo[b,e]azepin-11-yl]acetic acid

1 mg; ESI-MS  $[M+H^+] = 438$ .

45 Example I.B.98

[5-(2-{[2-(Dimethylamino)ethyl]amino}-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]acetic acid

1 mg; ESI-MS  $[M+H]^+$  = 396.

5

Example I.B.99

[5-(2-{[4-(Dimethylamino)butyl]amino}-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]acetic acid

10 1 mg; ESI-MS  $[M+H]^+$  = 424.

Example I.B.100

Methyl (3E/Z)-3-(5-{2-[4-[(benzylamino)carbonyl]amino]benzyl)-amino}-2-oxoethyl)-6-oxo-5,6-dihydro-11H-dibenzo[b,e]azepin-11-yliden)propanoate

Coupling of (11Z/E)-11-(3-methoxy-3-oxopropylidene)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-5-yl]acetate (69) with N-[4-(aminomethyl)phenyl]-N'-benzylurea (trifluoroacetate) (58) using HATU as coupling reagent afforded 65 mg; ESI-MS  $[M+K]^+$  = 627.5,  $[M+H]^+$  = 589.3.

Example I.B.101

(3E/Z)-3-(5-{2-[4-[(benzylamino)carbonyl]amino]benzyl)amino}-2-oxoethyl)-6-oxo-5,6-dihydro-11H-dibenzo[b,e]azepin-11-ylidene)-propanoic acid

Hydrolysis of the methyl ester from Example I.B.100 and purification of the crude product by chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH 0 to 20%) afforded 21 mg; ESI-MS  $[M+K]^+$  = 613.2,  $[M+Na]^+$  = 597.2,  $[M+H]^+$  = 575.2.

Example I.B.102

Methyl 3-(5-{2-[4-[(benzylamino)carbonyl]amino]benzyl)amino}-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl)-propanoate

Coupling of 11-(3-methoxy-3-oxopropyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-5-yl acetate (70) with N-[4-(aminomethyl)phenyl]-N'-benzylurea (trifluoroacetate) (58) using HATU as coupling reagent afforded 140 mg; ESI-MS  $[M+K]^+$  = 629.2,  $[M+H]^+$ : 591.25, 296.1.

Example I.B.103

45



3-(5-{2-[(4-[(benzylamino)carbonyl]amino)benzyl]amino}-2-oxo-ethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl)propanoic acid

- 5 Hydrolysis of the methyl ester from Example I.B.102 afforded 83 mg of the title compound; ESI-MS [M+K<sup>+</sup>] = 615.2, [M+H<sup>+</sup>]: 577.25, 289.1.

Example I.B.104

- 10 Methyl 3-[6-oxo-5-(2-oxo-2-{[2-(2-pyridinylamino)ethyl]amino}ethyl)-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]propanoate

Coupling of

- 11-(3-methoxy-3-oxopropyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]-  
15 azepin-5-yl acetate (70) with N<sup>1</sup>-(2-pyridinyl)-1,2-ethanediamine and purification of the crude product by chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH 0 to 5%) afforded 3 mg; ESI-MS [M+H<sup>+</sup>]: 473.

Example I.B.105

- 20 3-[6-Oxo-5-(2-oxo-2-{[2-(2-pyridinylamino)ethyl]amino}ethyl)-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]propanoic acid (Na salt)

Hydrolysis of the methyl ester from Example I.B.102 afforded 3 mg of the title compound; ESI-MS [M+K<sup>+</sup>] = 497.1, [M+H<sup>+</sup>]: 459.15.

25

Example I.B.106

Methyl (2E/Z)-(5-{2-[(4-[(benzylamino)carbonyl]amino)benzyl]-amino}-2-oxoethyl)-4-oxo-4,5-dihydro-10H-thieno[3,4-c][1]-benzazepin-10-ylidene)ethanoate

30

Coupling of (10E/Z)-10-(2-methoxy-2-oxoethylidene)-4-oxo-4H-thieno[3,4-c][1]benzazepin-5(10H)-yl acetate (71) with N-[4-(aminomethyl)phenyl]-N'-benzylurea (trifluoroacetate) (58) afforded 98 mg; ESI-MS [M+K<sup>+</sup>] = 619.2, [M+H<sup>+</sup>] = 581.15, 291.1.

35

Example I.B.107

(2E)-(5-{2-[(4-[(benzylamino)carbonyl]amino)benzyl]amino}-2-oxoethyl)-4-oxo-4,5-dihydro-10H-thieno[3,4-c][1]benzazepin-10-ylidene)ethanoic acid

40

Hydrolysis of the methyl ester I.B.106 afforded 24 mg of the title compound; ESI-MS [M+K<sup>+</sup>] = 605.15, [M+H<sup>+</sup>]: 567.15, 284.2.

Example I.B.108

45

Methyl [5-(2-{[4-(1*H*-benzimidazol-2-ylamino)benzyl]amino}-2-oxoethyl)-4-oxo-5,10-dihydro-4*H*-thieno[3,4-*c*][1]benzazepin-10-yl]acetate

- 5 Coupling of 10-(2-methoxy-2-oxoethyl)-4-oxo-4*H*-thieno[3,4-*c*]-[1]benzazepin-5(10*H*)-yl acetate (72) with *N*-[4-(aminomethyl)-phenyl]-1*H*-benzimidazol-2-amine (hydrochloride) (47) and purification of the crude product by chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH 0 to 2 %) afforded 47 mg; ESI-MS [M+H<sup>+</sup>]: 566.2.

10

Example I.B.109

[5-(2-{[4-(1*H*-Benzimidazol-2-ylamino)benzyl]amino}-2-oxoethyl)-4-oxo-5,10-dihydro-4*H*-thieno[3,4-*c*][1]benzazepin-10-yl]acetate

- 15 Hydrolysis of the methyl ester I.B.108 afforded 9 mg of the title compound; ESI-MS [M+H<sup>+</sup>]: 552.22.

Example I.B.110

- Methyl (2*E/Z*)-(4-{2-[(4-{[(benzylamino)carbonyl]amino}benzyl)-2-amino]-2-oxoethyl}-5-oxo-4,5-dihydro-9*H*-dithieno[3,4-*b*:3,4-*e*]azepin-9-ylidene)ethanoate

- 25 Coupling of (9*E/Z*)-9-(2-methoxy-2-oxoethylidene)-5-oxo-9*H*-dithieno[3,4-*b*:3,4-*e*]azepin-4(5*H*)-yl acetate (73) with *N*-[4-(aminomethyl)phenyl]-*N'*-benzylurea (trifluoroacetate) (58) afforded 55 mg of the title compound; ESI-MS [M+K<sup>+</sup>] = 625.05, [M+H<sup>+</sup>]: 587.15.

Example I.B.111

- 30 (2*E/Z*)-(4-{2-[(4-{[(benzylamino)carbonyl]amino}benzyl)amino]-2-oxoethyl}-5-oxo-4,5-dihydro-9*H*-dithieno[3,4-*b*:3,4-*e*]azepin-9-ylidene)ethanoic acid

- Hydrolysis of the methyl ester I.B.110 afforded 10 mg of the  
35 title compound; ESI-MS [M+K<sup>+</sup>] = 611.0, [M+H<sup>+</sup>]: 573.2, 129.15, 100.2.

Example I.B.112

Methyl

- 40 [4-(2-{[4-(1*H*-Benzimidazol-2-ylamino)benzyl]amino}-2-oxoethyl)-5-oxo-4,5-dihydro-9*H*-dithieno[3,4-*b*:3,4-*e*]azepin-9-yl]-acetate

## 132

Coupling of (9-(2-methoxy-2-oxoethyl)-5-oxo-9H-dithieno-[3,4-b:3,4-e]azepin-4(5H)-yl acetate (74) with N-[4-(aminomethyl)phenyl]-1H-benzimidazol-2-amine (hydrochloride) (47) afforded 21 mg of the title compound; ESI-MS [M+H<sup>+</sup>]: 573.

5

## Example I.B.113

Sodium [4-(2-([4-(1H-benzimidazol-2-ylamino)benzyl]amino)-2-oxoethyl)-5-oxo-4,5-dihydro-9H-dithieno[3,4-b:3,4-e]azepin-9-yl]acetate

10

Hydrolysis of the methyl ester I.B.112 afforded 10 mg of the title compound; ESI-MS [M+H<sup>+</sup>]: 558.05, 502.1.

## Example I.B.114

15 5-([4-([4-(1H-Benzimidazol-2-yl)benzyl]amino)carbonyl]-1,3-thiazol-2-yl)methyl]-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl acetate

Coupling of 2-([11-(2-tert-butoxy-2-oxoethyl)-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-5-yl)methyl]-1,3-thiazole-4-carboxylic acid (75) with [4-(1H-benzimidazol-2-yl)benzyl]methylamine from building block 14 afforded 15 mg of the title compound ESI-MS [M+H<sup>+</sup>]: 614.25.

20

25 The following were prepared in analogy to I.B.114:

## Example I.B.115

6-Oxo-5-([4-([4-((2-pyridinylamino)methyl)-1-piperidinyl]-carbonyl)-1,3-thiazol-2-yl)methyl]-6,11-dihydro-5H-dibenzo[b,e]-azepin-11-yl acetate

30

60 mg; ESI-MS [M+H<sup>+</sup>]: 528.25.

## Example I.B.116

35 5-([4-([4-([4-(Benzylamino)carbonyl]amino)benzyl]amino)-carbonyl]-1,3-thiazol-2-yl)methyl]-6-oxo-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl acetate

25 mg; ESI-MS [M+H<sup>+</sup>]: 646.25.

40

## Example I.B.117

6-Oxo-5-([4-([4-([4-((2-pyridinylamino)methyl)benzyl]amino)-carbonyl]-1,3-thiazol-2-yl)methyl]-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl acetate

45

15 mg; ESI-MS [M+H<sup>+</sup>]: 604.15.

## Example I.B.118

6-Oxo-5-[(4-[(4-[(2-pyridinylamino)methyl]-2-thienyl)methyl]-amino]carbonyl)-1,3-thiazol-2-yl)methyl]-6,11-dihydro-5H-dibenzo-[b,e]azepin-11-yl acetate

5

70 mg; ESI-MS  $[M+H^+]$ : 610.15.

## II. Biological examples

## 10 Example 1

Integrin  $\alpha_v\beta_3$  assay

Integrin  $\alpha_v\beta_3$  antagonists were identified and assessed by using an assay system based on competition between the natural integrin

15  $\alpha_v\beta_3$  ligand vitronectin and the test substance for binding to solid phase-bound integrin  $\alpha_v\beta_3$ .

## Procedure

- 20 - Coat microtiter plates with 250 ng/ml integrin  $\alpha_v\beta_3$  in 0.05 M  $\text{NaHCO}_3$  pH 9.2; 0.1 ml/well;
- saturate with 1% milk powder/assay buffer; 0.3 ml/well; 0.5 h/RT
- 25 - wash 3x with 0.05% Tween 20/assay buffer
- test substance in 0.1% milk powder/assay buffer, 50  $\mu\text{l}$ /well + 0  $\mu\text{g}/\text{ml}$  or 2  $\mu\text{g}/\text{ml}$  human vitronectin (Boehringer Ingelheim
- 30 T007) in 0.1% milk powder/assay buffer, 50  $\mu\text{l}$ /well; 1 h/RT
- wash 3x with 0.05% Tween 20/assay buffer
- 1  $\mu\text{g}/\text{ml}$  anti-human vitronectin antibody coupled to peroxidase
- 35 (Kordia SAVN-APHRP) in 0.1% milk powder/assay buffer; 0.1 ml/well; 1 h/RT
- wash 3x with 0.05% Tween 20/assay buffer
- 40 - 0.1 ml/well peroxidase substrate
- stop reaction with 0.1 ml/well 2 M  $\text{H}_2\text{SO}_4$
- measure absorption at 450 nm

45

Integrin  $\alpha_v\beta_3$ : human placenta is solubilized with Nonidet, and integrin  $\alpha_v\beta_3$  is affinity-purified on a GRGDSPK matrix (elution with EDTA). Contamination by integrin  $\alpha_{IIb}\beta_3$  and human serum albumin, and the detergent and EDTA, are removed by anion exchange chromatography.

Assay buffer: 50 mM Tris pH 7.5; 100 mM NaCl; 1 mM  $\text{CaCl}_2$ ; 1 mM  $\text{MgCl}_2$ ; 10  $\mu\text{M}$   $\text{MnCl}_2$   
 Peroxidase substrate: mix 0.1 ml of TMB solution (42 mM TMB in 10 DMSO) and 10 ml of substrate buffer (0.1 M Na acetate, pH 4.9) and then add 14.7  $\mu\text{l}$  of 3%  $\text{H}_2\text{O}_2$ .

Various dilutions of the test substances are used in the assay, and the  $\text{IC}_{50}$  values are determined (concentration of the antagonist at which 50% of the ligand is displaced). The compounds of Examples I.B.37, I.B.46, I.B.52 and I.B.118 showed the best results in this.

#### Example 2

#### 20 Integrin $\alpha_{IIb}\beta_3$ assay

The assay is based on competition between the natural integrin  $\alpha_{IIb}\beta_3$  ligand fibrinogen and the test substance for binding to integrin  $\alpha_{IIb}\beta_3$ .

25

#### Procedure

- coat microtiter plates with 10  $\mu\text{g}/\text{ml}$  fibrinogen (Calbiochem 341578) in 0.05 M  $\text{NaHCO}_3$  pH 9.2; 0.1 ml/well;
- 30 - saturate with 1% BSA/PBS; 0.3 ml/well; 30 min/RT
- wash 3x with 0.05% Tween 20/PBS
- 35 - test substance in 0.1% BSA/PBS; 50  $\mu\text{l}/\text{well}$  +  
 200  $\mu\text{g}/\text{ml}$  integrin  $\alpha_{IIb}\beta_3$  (Kordia) in 0.1% BSA/PBS; 50  $\mu\text{l}/\text{well}$ ;  
 2 to 4 h/RT
- wash 3x as above
- 40 - biotinylated anti-integrin  $\alpha_{IIb}\beta_3$  antibody (Dianova CBL 130 B);  
 1:1000 in 0.1% BSA/PBS; 0.1 ml/well; 2 to 4 h/RT
- wash 3x as above
- 45

- streptavidin-peroxidase complex (B.M. 1089153) 1:10,000 in 0.1% BSA/PBS; 0.1 ml/well; 30 min/RT
- wash 3x as above
- 5 - 0.1 ml/well peroxidase substrate
- stop reaction with 0.1 ml/well 2 M H<sub>2</sub>SO<sub>4</sub>
- 10 - measure the absorption at 450 nm

Peroxidase substrate: mix 0.1 ml of TMB solution (42 mM TMB in DMSO) and 10 ml of substrate buffer (0.1 M Na acetate pH 4.9) and then add 14.7  $\mu$ l of 3% H<sub>2</sub>O<sub>2</sub>

- 15 Various dilutions of the test substances are used in the assay, and the IC<sub>50</sub> values are determined (concentration of the antagonist at which 50% of the ligand is displaced). The selectivity of the substances can be determined by comparing
- 20 the IC<sub>50</sub> values in the integrin  $\alpha_{11b}\beta_3$  and integrin  $\alpha_v\beta_3$  assays.

#### Example 3

##### CAM assay

- 25 The CAM (chorioallantoic membrane) assay is a generally accepted model for assessing the in vivo activity of integrin  $\alpha_v\beta_3$  antagonists. It is based on the inhibition of angiogenesis and neovascularization of tumor tissue (Am. J. Pathol. 1975, 79, 597-618; Cancer Res. 1980, 40, 2300-2309; Nature 1987, 329, 630).
- 30 The procedure is analogous to the prior art. The growth of chicken embryo blood vessels and of transplanted tumor tissue is easy to follow and assess.

#### Example 4

##### 35 Rabbit eye assay

- It is possible in this in vivo model to follow and assess in analogy to Example 3 the inhibition of angiogenesis and neovascularization in the presence of integrin  $\alpha_v\beta_3$  antagonists.
- 40 The model is generally accepted and is based on growth of blood vessels starting from the edge into the cornea of the rabbit eye (Proc. Natl. Acad. Sci. USA. 1994, 91, 4082-4085; Science 1976, 193, 70-72). The procedure is analogous to the prior art.

We claim:

1. A compound of the formula I

5



I

where B, G and L have the following meanings:

10

L a structural element of the formula  $I_L$

 $I_L$ 

where

15

T is a COOH group or a radical which can be hydrolyzed to COOH and

20

-U- is  $-(X_L)_a-(CR_L^1R_L^2)_b-$ ,  $-CR_L^1=CR_L^2-$ , ethynylene or  $=CR_L^1-$ , where

a is 0 or 1,

b is 0, 1 or 2

25

$X_L$  is  $CR_L^3R_L^4$ ,  $NR_L^5$ , oxygen or sulfur,

$R_L^1$ ,  $R_L^2$ ,  $R_L^3$ ,  $R_L^4$

30

are, independently of one another, hydrogen, -T, -OH,  $-NR_L^6R_L^7$ ,  $-CO-NH_2$ , a halogen radical, a branched or unbranched, optionally substituted  $C_1-C_6$ -alkyl,  $C_2-C_6$ -alkenyl,  $C_2-C_6$ -alkynyl,  $C_3-C_7$ -cycloalkyl,  $-CO-NH(C_1-C_6-alkyl)$ ,  $-CO-N(C_1-C_6-alkyl)_2$  or  $C_1-C_4$ -alkoxy radical, an optionally substituted  $C_1-C_2$ -alkylene-T,  $C_2$ -alkenylene-T or  $C_2$ -alkynylene-T radical, an optionally substituted aryl or arylalkyl radical or, in each case independently of one another, two radicals  $R_L^1$  and  $R_L^2$  or  $R_L^3$  and  $R_L^4$  or, where appropriate,  $R_L^1$  and  $R_L^3$  together are an optionally substituted 3- to 7-membered saturated or unsaturated carbocyclic or heterocyclic system which may contain up to three different or identical heteroatoms O, N, S,

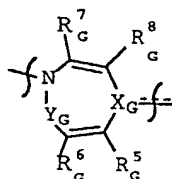
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$R_L^5$ ,  $R_L^6$ ,  $R_L^7$

are, independently of one another, hydrogen, a branched or unbranched, optionally substituted

C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, CO-O-C<sub>1</sub>-C<sub>6</sub>-alkyl, SO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub>-alkyl or CO-C<sub>1</sub>-C<sub>6</sub>-alkyl radical or an optionally substituted CO-O-alkylene-aryl, SO<sub>2</sub>-aryl, CO-aryl, SO<sub>2</sub>-alkylene-aryl or CO-alkylene-aryl radical,

G a structural element of the formula I<sub>G</sub>

I<sub>G</sub>

where

the structural element G can be incorporated in both orientations, and

X<sub>G</sub> is nitrogen or CR<sub>G</sub><sup>1</sup> in the case where structural element G is connected to structural element L or B via X<sub>G</sub> by a single bond,

or

is carbon in the case where structural element G is connected to structural element L via X<sub>G</sub> by a double bond,

Y<sub>G</sub> is CO, CS, C=NR<sub>G</sub><sup>2</sup> or CR<sub>G</sub><sup>3</sup>R<sub>G</sub><sup>4</sup>,

where

R<sub>G</sub><sup>1</sup> is hydrogen, halogen, a hydroxyl group or a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl or C<sub>1</sub>-C<sub>4</sub>-alkoxy radical,

R<sub>G</sub><sup>2</sup> is hydrogen, a hydroxyl group, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl or -O-C<sub>3</sub>-C<sub>7</sub>-cycloalkyl radical or an optionally substituted aryl, -O-aryl, arylalkyl or -O-alkylene-aryl radical and

R<sub>G</sub><sup>3</sup>, R<sub>G</sub><sup>4</sup>

are, independently of one another, hydrogen or a branched or unbranched, optionally substituted





is present where appropriate or all carbons to be substituted,  
with the proviso that at least one heteroatom selected from the group of O, N or S is present in the structural element A,

or

a 9- to 14-membered polycyclic saturated, unsaturated or aromatic system having up to 6 heteroatoms selected from the group of N, O or S, it being possible, in each case independently of one another, for the ring nitrogen which is present where appropriate or all carbons to be substituted,  
with the proviso that at least one heteroatom selected from the group of O, N or S is present in the structural element A,

or

a radical



where

$Z_A^1$  is oxygen, sulfur or optionally substituted nitrogen and

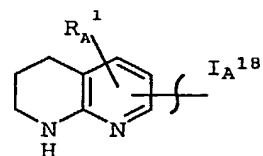
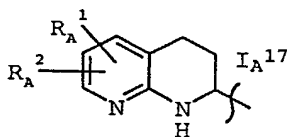
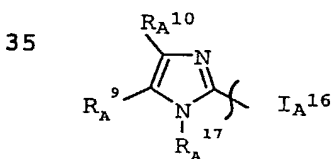
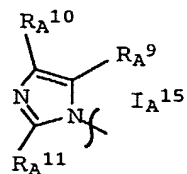
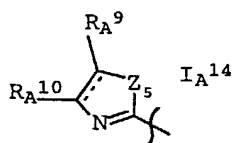
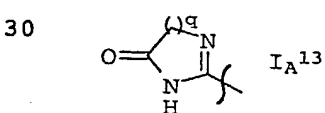
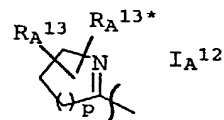
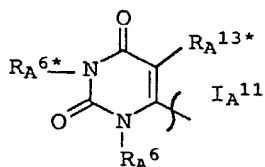
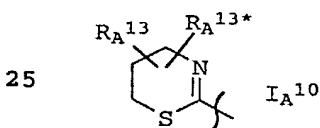
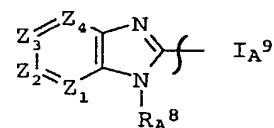
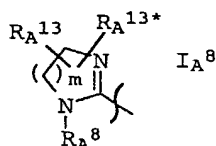
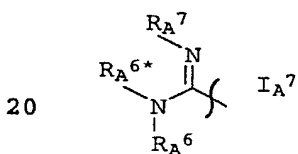
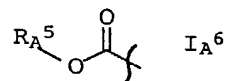
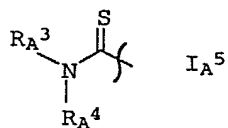
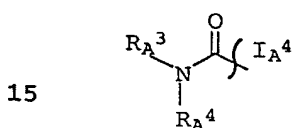
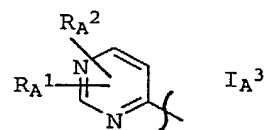
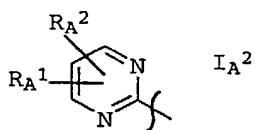
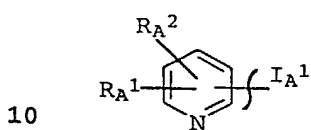
$Z_A^2$  is optionally substituted nitrogen, oxygen or sulfur,

and

E a spacer structural element which connects structural element A to structural element G covalently, where the number of atomic bonds along the shortest possible route along the structural element framework E is from 4 to 12.

3. A compound as claimed in either of claims 1 or 2, wherein the structural element used as structural element A is selected from the group of structural elements of the formulae I<sub>A</sub><sup>1</sup> to I<sub>A</sub><sup>18</sup>,

5



40

where

m, p, q

are, independently of one another, 1, 2 or 3,

45

$R_A^{11}$ ,  $R_A^{12}$

are, independently of one another, hydrogen, CN, halogen, a branched or unbranched, optionally substituted  $C_1$ - $C_6$ -alkyl or CO- $C_1$ - $C_6$ -alkyl radical or an optionally substituted aryl, arylalkyl, hetaryl, hetarylalkyl or  $C_3$ - $C_7$ -cycloalkyl radical or a radical CO-O- $R_A^{14}$ , O- $R_A^{14}$ , S- $R_A^{14}$ ,  $NR_A^{15}R_A^{16}$ , CO- $NR_A^{15}R_A^{16}$  or  $SO_2NR_A^{15}R_A^{16}$  or the two  $R_A^{11}$  and  $R_A^{12}$  radicals together are a fused-on, optionally substituted 5- or 6-membered, unsaturated or aromatic carbocyclic or heterocyclic system which may contain up to three heteroatoms selected from the group of O, N, or S,

$R_A^{13}$ ,  $R_A^{13*}$

are, independently of one another, hydrogen, CN, halogen, a branched or unbranched, optionally substituted  $C_1$ - $C_6$ -alkyl radical or an optionally substituted aryl, arylalkyl, hetaryl,  $C_3$ - $C_7$ -cycloalkyl radical or a CO-O- $R_A^{14}$ , O- $R_A^{14}$ , S- $R_A^{14}$ ,  $NR_A^{15}R_A^{16}$  or CO- $NR_A^{15}R_A^{16}$  radical,

where

$R_A^{14}$  is hydrogen, a branched or unbranched, optionally substituted  $C_1$ - $C_6$ -alkyl, alkylene- $C_1$ - $C_4$ -alkoxy,  $C_2$ - $C_6$ -alkenyl,  $C_2$ - $C_6$ -alkynyl or alkylene-cycloalkyl radical or an optionally substituted  $C_3$ - $C_7$ -cycloalkyl, aryl, arylalkyl, hetaryl or hetarylalkyl radical,

$R_A^{15}$ ,  $R_A^{16}$ ,

are, independently of one another, hydrogen, a branched or unbranched, optionally substituted  $C_1$ - $C_6$ -alkyl, CO- $C_1$ - $C_6$ -alkyl,  $SO_2$ - $C_1$ - $C_6$ -alkyl, COO- $C_1$ - $C_6$ -alkyl, arylalkyl, COO-alkylene-aryl,  $SO_2$ -alkylene-aryl or hetarylalkyl radical or an optionally substituted  $C_3$ - $C_7$ -cycloalkyl, aryl, CO-aryl,  $SO_2$ -aryl, hetaryl or CO-hetaryl radical,

$R_A^{13}$ ,  $R_A^{14}$

are, independently of one another, hydrogen,  $-(CH_2)_n-(X_A)_j-R_A^{12}$ , or the two radicals together are a 3- to 8-membered, saturated, unsaturated or aromatic N heterocyclic system which may additionally contain two other identical or different heteroatoms O, N or S, it being possible for the ring optionally to be substituted

or for another, optionally substituted, saturated, unsaturated or aromatic ring to be fused onto this ring,

where

- 5
- n can be 0, 1, 2 or 3,
- j can be 0 or 1,
- 10  $X_A$  can be  $-SO_2-$ ,  $-S-$ ,  $-O-$ ,  $-CO-$ ,  $-O-CO-$ ,  $-CO-O-$ ,  $-CO-N(R_A^{12})-$ ,  $-N(R_A^{12})-CO-$ ,  $-N(R_A^{12})-SO_2-$  or  $-SO_2-N(R_A^{12})-$  and
- 15  $R_A^{12}$  can be hydrogen, a branched or unbranched, optionally substituted  $C_1-C_6$ -alkyl,  $C_1-C_4$ -alkoxy,  $-O$ -alkylene-aryl or  $-O$ -aryl radical, an amino radical with primary or, where appropriate, secondary or tertiary substitution, an optionally  $C_1-C_4$ -alkyl- or aryl-substituted  $C_2-C_6$ -alkynyl or  $C_2-C_6$ -alkenyl
- 20 radical or a 3- to 6-membered, saturated or unsaturated heterocyclic system which is substituted by up to three identical or different radicals and which may contain up to three different or identical heteroatoms O, N, S,  $C_3-C_7$ -cycloalkyl, aryl or
- 25 hetaryl radical, it being possible for two radicals together to be a fused-on, saturated, unsaturated or aromatic carbocyclic or heterocyclic system which may contain up to three different or identical
- 30 heteroatoms O, N, S, and the ring may optionally be substituted, or another, optionally substituted, saturated, unsaturated or aromatic ring may be fused onto this ring,
- 35  $R_A^5$  is a branched or unbranched, optionally substituted  $C_1-C_6$ -alkyl, arylalkyl,  $C_3-C_7$ -cycloalkyl or  $C_1-C_6$ -alkyl- $C_3-C_7$ -cycloalkyl radical or an optionally substituted aryl radical,
- 40  $R_A^6$ ,  $R_A^{6*}$  are hydrogen, a branched or unbranched, optionally substituted  $C_1-C_4$ -alkyl,  $-CO-O-C_1-C_4$ -alkyl, arylalkyl,  $-CO-O$ -alkylene-aryl,  $-CO-O$ -allyl,  $-CO-C_1-C_4$ -alkyl,  $-CO$ -alkylene-aryl,  $C_3-C_7$ -cycloalkyl or  $-CO$ -allyl radical or the two radicals  $R_A^6$  and  $R_A^{6*}$  in the structural element
- 45  $I_A^7$  together are an optionally substituted, saturated, unsaturated or aromatic heterocyclic system which may, in

addition to the ring nitrogen, contain up to two further different or identical heteroatoms O, N, S,

- 5  $R_A^7$  is hydrogen, -OH, -CN, -CONH<sub>2</sub>, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl or -O-CO-C<sub>1</sub>-C<sub>4</sub>-alkyl radical, or an optionally substituted arylalkyl, -O-alkylene-aryl, -O-CO-aryl, -O-CO-alkylene-aryl or -O-CO-allyl radical, or the two radicals  $R_A^6$  and  $R_A^7$  together are an optionally substituted, unsaturated or aromatic heterocyclic system which may, in addition to the ring nitrogen, contain up to two further different or identical heteroatoms O, N, S,
- 10
- 15  $R_A^8$  is hydrogen, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>4</sub>-alkyl, CO-C<sub>1</sub>-C<sub>4</sub>-alkyl, SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub>-alkyl or CO-O-C<sub>1</sub>-C<sub>4</sub>-alkyl radical or an optionally substituted aryl, CO-aryl, SO<sub>2</sub>-aryl, CO-O-aryl, CO-alkylene-aryl, SO<sub>2</sub>-alkylene-aryl, CO-O-alkylene-aryl or alkylene-aryl radical,
- 20
- $R_A^9$ ,  $R_A^{10}$  are, independently of one another, hydrogen, -CN, halogen, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl radical or an optionally substituted aryl, arylalkyl, hetaryl, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl radical or a CO-O- $R_A^{14}$ , O- $R_A^{14}$ , S- $R_A^{14}$ , NR<sub>A</sub><sup>15</sup> $R_A^{16}$  or CO-NR<sub>A</sub><sup>15</sup> $R_A^{16}$  radical, or the two  $R_A^9$  and  $R_A^{10}$  radicals in the structural element I<sub>A</sub><sup>14</sup> together are a 5- to 7-membered saturated, unsaturated or aromatic carbocyclic or heterocyclic system which may contain up to three different or identical heteroatoms O, N, S and is optionally substituted by up to three identical or different radicals,
- 25
- 30
- 35  $R_A^{11}$  is hydrogen, -CN, halogen, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl radical or an optionally substituted aryl, arylalkyl, hetaryl, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl radical or a CO-O- $R_A^{14}$ , O- $R_A^{14}$ , S- $R_A^{14}$ , NR<sub>A</sub><sup>15</sup> $R_A^{16}$  or CO-NR<sub>A</sub><sup>15</sup> $R_A^{16}$  radical,
- 40
- $R_A^{17}$  in the structural element I<sub>A</sub><sup>16</sup> the two radicals  $R_A^9$  and  $R_A^{17}$  together are a 5- to 7-membered saturated, unsaturated or aromatic heterocyclic system which may, in addition to the ring nitrogen, contain up to three different or identical heteroatoms O, N, S, and is
- 45

optionally substituted by up to three identical or different radicals,

$Z^1, Z^2, Z^3, Z^4$

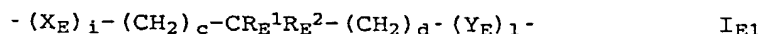
5 are, independently of one another, nitrogen, C-H, C-halogen or a branched or unbranched, optionally substituted C-C<sub>1</sub>-C<sub>4</sub>-alkyl or C-C<sub>1</sub>-C<sub>4</sub>-alkoxy radical,

$Z^5$  is NR<sub>A</sub><sup>8</sup>, oxygen or sulfur.

10

4. A compound as claimed in any of claims 1 to 3, wherein the spacer structural element E is composed of two to four partial structural elements selected from the group of E<sup>1</sup> and E<sup>2</sup>, the partial structural elements being linked in any sequence, and E<sup>1</sup> and E<sup>2</sup> having the following meanings:

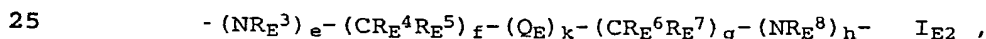
E<sup>1</sup> a partial structural element of the formula I<sub>E1</sub>



20

and

E<sup>2</sup> a partial structural element of the formula I<sub>E2</sub>



25

where

c, d, f, g

30

are, independently of one another, 0, 1 or 2,

e, h, i, k, l,

are, independently of one another, 0 or 1,

35

X<sub>E</sub>, Q<sub>E</sub>

are, independently of one another, CO, CO-NR<sub>E</sub><sup>9</sup>, S, SO, SO<sub>2</sub>, SO<sub>2</sub>NR<sub>E</sub><sup>9</sup>, CS, CS-NR<sub>E</sub><sup>9</sup>, CS-O, CO-O, O-CO, O, ethynyl, CR<sub>E</sub><sup>10</sup>-O-CR<sub>E</sub><sup>11</sup>, CR<sub>E</sub><sup>10</sup>R<sub>E</sub><sup>11</sup>, C(=CR<sub>E</sub><sup>10</sup>R<sub>E</sub><sup>11</sup>), CR<sub>E</sub><sup>10</sup>=CR<sub>E</sub><sup>11</sup>, CR<sub>E</sub><sup>10</sup>(OR<sub>E</sub><sup>12</sup>)-CR<sub>E</sub><sup>11</sup>, CR<sub>E</sub><sup>10</sup>-CR<sub>E</sub><sup>11</sup>(OR<sub>E</sub><sup>12</sup>) or an optionally substituted 4- to 11-membered mono- or polycyclic aliphatic or aromatic hydrocarbon which may contain up to 6 double bonds and up to 6 heteroatoms selected from the group of N, O, S,

40

45

Y<sub>E</sub> is -CO-, -NR<sub>E</sub><sup>9</sup>-CO-, -SO-, -SO<sub>2</sub>-, -NR<sub>E</sub><sup>9</sup>-SO<sub>2</sub>-, -CS-, -NR<sub>E</sub><sup>9</sup>-CS-, -O-CS- or -O-CO-

$R_E^1, R_E^2, R_E^4, R_E^5, R_E^6, R_E^7$ 

are, independently of one another, hydrogen, halogen, a hydroxyl group, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkynyl or alkylene-cycloalkyl radical, a -(CH<sub>2</sub>)<sub>w</sub>-R<sub>E</sub><sup>13</sup> radical, an optionally substituted C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, aryl, arylalkyl, hetaryl, hetarylalkyl, O-aryl or O-alkylene-aryl radical, or, independently of one another, in each case two radicals R<sub>E</sub><sup>1</sup> and R<sub>E</sub><sup>2</sup> or R<sub>E</sub><sup>4</sup> and R<sub>E</sub><sup>5</sup> or R<sub>E</sub><sup>6</sup> and R<sub>E</sub><sup>7</sup> together are a 3- to 7-membered, optionally substituted, saturated or unsaturated carbocyclic system,

where

w is 0, 1, 2, 3 or 4,

 $R_E^3, R_E^8, R_E^9$ 

are, independently of one another, hydrogen, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl, CO-C<sub>1</sub>-C<sub>6</sub>-alkyl, CO-O-C<sub>1</sub>-C<sub>6</sub>-alkyl or SO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub>-alkyl radical or an optionally substituted C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, CO-O-alkylene-aryl, CO-alkylene-aryl, CO-aryl, SO<sub>2</sub>-aryl, CO-hetaryl or SO<sub>2</sub>-alkylene-aryl radical,

 $R_E^{10}, R_E^{11}$ 

are, independently of one another, hydrogen, a hydroxyl group, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkynyl or alkylene-cycloalkyl radical or an optionally substituted C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, aryl, arylalkyl, hetaryl or hetarylalkyl radical,

R<sub>E</sub><sup>12</sup> is hydrogen, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkynyl or alkylene-cycloalkyl radical or an optionally substituted C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, aryl, arylalkyl, hetaryl or hetarylalkyl radical,

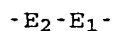
R<sub>E</sub><sup>13</sup> is hydrogen, a hydroxyl group, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, -arylalkyl, -O-alkylene-aryl or -O-aryl radical, an amino radical with primary or, where appropriate, secondary or tertiary substitution, an optionally C<sub>1</sub>-C<sub>4</sub>-alkyl- or aryl-substituted



- 5 C<sub>2</sub>-C<sub>6</sub>-alkynyl or C<sub>2</sub>-C<sub>6</sub>-alkenyl radical, a  
 C<sub>5</sub>-C<sub>12</sub>-bicycloalkyl, C<sub>6</sub>-C<sub>18</sub>-tricycloalkyl radical, a  
 CO-O-R<sub>A</sub><sup>14</sup> radical, or a 3- to 6-membered, saturated  
 or unsaturated heterocyclic system which is  
 substituted by up to three identical or different  
 radicals and which may contain up to three different  
 or identical heteroatoms O, N, S,  
 C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, aryl or hetaryl radical, it being  
 possible for two radicals together to be a fused-on,  
 10 saturated, unsaturated or aromatic carbocyclic or  
 heterocyclic system which may contain up to three  
 different or identical heteroatoms O, N, S, and the  
 ring may optionally be substituted or another,  
 optionally substituted, saturated, unsaturated or  
 15 aromatic ring may be fused onto this ring.

5. A compound as claimed in any of claims 1 to 4, wherein the  
 spacer structural element E used is a structural element of  
 the formula I<sub>E1E2</sub>

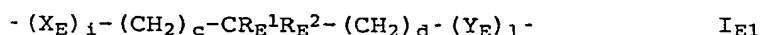
20

I<sub>E1E2</sub>

and E<sup>1</sup> and E<sup>2</sup> have the following meanings:

25

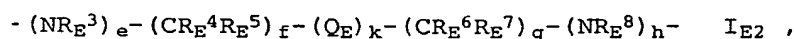
E<sup>1</sup> a partial structural element of the formula I<sub>E1</sub>



and

30

E<sup>2</sup> a partial structural element of the formula I<sub>E2</sub>



35

where

c, d, f, g

are, independently of one another, 0, 1 or 2,

40

e, h, i, k, l

are, independently of one another, 0 or 1,

X<sub>E</sub>, Q<sub>E</sub>

45

are, independently of one another, CO, CO-NR<sub>E</sub><sup>9</sup>, S,  
 SO, SO<sub>2</sub>, SO<sub>2</sub>NR<sub>E</sub><sup>9</sup>, CS, CS-NR<sub>E</sub><sup>9</sup>, CS-O, CO-O, O-CO, O,  
 ethynyl, CR<sub>E</sub><sup>10</sup>-O-CR<sub>E</sub><sup>11</sup>, CR<sub>E</sub><sup>10</sup>R<sub>E</sub><sup>11</sup>, C(=CR<sub>E</sub><sup>10</sup>R<sub>E</sub><sup>11</sup>),  
 CR<sub>E</sub><sup>10</sup>=CR<sub>E</sub><sup>11</sup>, CR<sub>E</sub><sup>10</sup>(OR<sub>E</sub><sup>12</sup>)-CR<sub>E</sub><sup>11</sup>, CR<sub>E</sub><sup>10</sup>-CR<sub>E</sub><sup>11</sup>(OR<sub>E</sub><sup>12</sup>) or an

optionally substituted 4- to 11-membered mono- or polycyclic aliphatic or aromatic hydrocarbon which may contain up to 6 double bonds and up to 6 heteroatoms selected from the group of N, O, S,

5

$Y_E$  is  $-CO-$ ,  $-NR_E^9-CO-$ ,  $-SO-$ ,  $-SO_2-$ ,  $-NR_E^9-SO_2-$ ,  $-CS-$ ,  $-NR_E^9-CS-$ ,  $-O-CS-$  or  $-O-CO-$

10

$R_E^1$ ,  $R_E^2$ ,  $R_E^4$ ,  $R_E^5$ ,  $R_E^6$ ,  $R_E^7$

are, independently of one another, hydrogen, halogen, a hydroxyl group, a branched or unbranched, optionally substituted  $C_1-C_6$ -alkyl,  $C_1-C_4$ -alkoxy,  $C_2-C_6$ -alkenyl,  $C_2-C_6$ -alkynyl or alkylene-cycloalkyl radical, a  $-(CH_2)_w-R_E^{13}$  radical, an optionally substituted  $C_3-C_7$ -cycloalkyl, aryl, arylalkyl, hetaryl, hetarylalkyl, O-aryl or O-alkylene-aryl radical, or, independently of one another, in each case two radicals  $R_E^1$  and  $R_E^2$  or  $R_E^4$  and  $R_E^5$  or  $R_E^6$  and  $R_E^7$  together are a 3- to 7-membered, optionally substituted, saturated or unsaturated carbocyclic system,

15

20

where

25

w is 0, 1, 2, 3 or 4,

30

$R_E^3$ ,  $R_E^8$ ,  $R_E^9$

are, independently of one another, hydrogen, a branched or unbranched, optionally substituted  $C_1-C_6$ -alkyl,  $CO-C_1-C_6$ -alkyl,  $CO-O-C_1-C_6$ -alkyl or  $SO_2-C_1-C_6$ -alkyl radical or an optionally substituted  $C_3-C_7$ -cycloalkyl,  $CO-O$ -alkylene-aryl,  $CO$ -alkylene-aryl,  $CO$ -aryl,  $SO_2$ -aryl,  $CO$ -hetaryl or  $SO_2$ -alkylene-aryl radical,

35

$R_E^{10}$ ,  $R_E^{11}$

are, independently of one another, hydrogen, a hydroxyl group, a branched or unbranched, optionally substituted  $C_1-C_6$ -alkyl,  $C_1-C_4$ -alkoxy,  $C_2-C_6$ -alkenyl,  $C_2-C_6$ -alkynyl or alkylene-cycloalkyl radical or an optionally substituted  $C_3-C_7$ -cycloalkyl, aryl, arylalkyl, hetaryl or hetarylalkyl radical,

40

45

$R_E^{12}$  is hydrogen, a branched or unbranched, optionally substituted  $C_1-C_6$ -alkyl,  $C_2-C_6$ -alkenyl,  $C_2-C_6$ -alkynyl or alkylene-cycloalkyl radical or an optionally

substituted C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, aryl, arylalkyl, hetaryl or hetarylalkyl radical,

R<sub>E</sub><sup>13</sup> is hydrogen, a hydroxyl group, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, arylalkyl, -O-alkylene-aryl or -O-aryl radical, an amino radical with primary or, where appropriate, secondary or tertiary substitution, an optionally C<sub>1</sub>-C<sub>4</sub>-alkyl- or aryl-substituted C<sub>2</sub>-C<sub>6</sub>-alkynyl or C<sub>2</sub>-C<sub>6</sub>-alkenyl radical, a C<sub>5</sub>-C<sub>12</sub>-bicycloalkyl, C<sub>6</sub>-C<sub>18</sub>-tricycloalkyl radical, a CO-O-R<sub>A</sub><sup>14</sup> radical, or a 3- to 6-membered, saturated or unsaturated heterocyclic system which is substituted by up to three identical or different radicals and which may contain up to three different or identical heteroatoms O, N, S, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, aryl or hetaryl radical, it being possible for two radicals together to be a fused-on, saturated, unsaturated or aromatic carbocyclic or heterocyclic system which may contain up to three different or identical heteroatoms O, N, S, and the ring may optionally be substituted, or another, optionally substituted, saturated, unsaturated or aromatic ring may be fused onto this ring.

6. The use of the structural element of the formula I<sub>GL</sub>

-G-L

I<sub>GL</sub>

to prepare compounds which bind to integrin receptors,

where G and L have the following meanings:

L a structural element of the formula I<sub>L</sub>

-U-T

I<sub>L</sub>

where

T is a COOH group or a radical which can be hydrolyzed to COOH and

-U- is -(X<sub>L</sub>)<sub>a</sub>-(CR<sub>L</sub><sup>1</sup>R<sub>L</sub><sup>2</sup>)<sub>b</sub>-, -CR<sub>L</sub><sup>1</sup>=CR<sub>L</sub><sup>2</sup>-, ethynylene or =CR<sub>L</sub><sup>1</sup>-, where

a is 0 or 1,

b is 0, 1 or 2

$X_L$  is  $CR_L^3R_L^4$ ,  $NR_L^5$ , oxygen or sulfur,

5  $R_L^1, R_L^2, R_L^3, R_L^4$

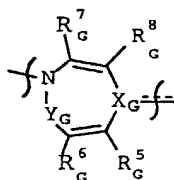
are, independently of one another, hydrogen, -T, -OH, - $NR_L^6R_L^7$ , -CO-NH<sub>2</sub>, a halogen radical, a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkynyl, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, 10 -CO-NH(C<sub>1</sub>-C<sub>6</sub>-alkyl), -CO-N(C<sub>1</sub>-C<sub>6</sub>-alkyl)<sub>2</sub> or C<sub>1</sub>-C<sub>4</sub>-alkoxy radical, an optionally substituted C<sub>1</sub>-C<sub>2</sub>-alkylene-T, C<sub>2</sub>-alkenylene-T or C<sub>2</sub>-alkynylene-T radical, an optionally substituted aryl or arylalkyl radical or, in each case independently of one 15 another, two radicals  $R_L^1$  and  $R_L^2$  or  $R_L^3$  and  $R_L^4$  or, where appropriate,  $R_L^1$  and  $R_L^3$  together are an optionally substituted 3- to 7-membered saturated or unsaturated carbocyclic or heterocyclic system which may contain up to three different or identical 20 heteroatoms O, N, S,

$R_L^5, R_L^6, R_L^7$

are, independently of one another, hydrogen, a branched or unbranched, optionally substituted 25 C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, CO-O-C<sub>1</sub>-C<sub>6</sub>-alkyl, SO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub>-alkyl or CO-C<sub>1</sub>-C<sub>6</sub>-alkyl radical or an optionally substituted CO-O-alkylene-aryl, SO<sub>2</sub>-aryl, CO-aryl, SO<sub>2</sub>-alkylene-aryl or CO-alkylene-aryl radical, 30

G a structural element of the formula I<sub>G</sub>

35



I<sub>G</sub>

40

where

the structural element G can be incorporated in both orientations, and

45

$X_G$  is nitrogen or  $CR_G^1$  in the case where structural element G is connected to structural element L or B via  $X_G$  by a single bond,

or

5 carbon in the case where structural element G is connected to structural element L via  $X_G$  by a double bond,

$Y_G$  is CO, CS,  $C=NR_G^2$  or  $CR_G^3R_G^4$ ,

10 where

15  $R_G^1$  is hydrogen, halogen, a hydroxyl group or a branched or unbranched, optionally substituted  $C_1$ - $C_6$ -alkyl or  $C_1$ - $C_4$ -alkoxy radical,

20  $R_G^2$  is hydrogen, a hydroxyl group, a branched or unbranched, optionally substituted  $C_1$ - $C_6$ -alkyl,  $C_1$ - $C_4$ -alkoxy,  $C_3$ - $C_7$ -cycloalkyl or -O- $C_3$ - $C_7$ -cycloalkyl radical or an optionally substituted aryl, -O-aryl, arylalkyl or -O-alkylene-aryl radical and

25  $R_G^3$ ,  $R_G^4$  are, independently of one another, hydrogen or a branched or unbranched, optionally substituted  $C_1$ - $C_6$ -alkyl,  $C_2$ - $C_6$ -alkenyl,  $C_2$ - $C_6$ -alkynyl or  $C_1$ - $C_4$ -alkoxy radical or the two  $R_G^3$  and  $R_G^4$  radicals together are a cyclic acetal -O-CH<sub>2</sub>-CH<sub>2</sub>-O- or -O-CH<sub>2</sub>-O- or the two  $R_G^3$  and  $R_G^4$  radicals together are an optionally substituted  $C_3$ - $C_7$ -cycloalkyl radical,

30  $R_G^5$ ,  $R_G^6$ ,  $R_G^7$ ,  $R_G^8$  are, independently of one another, hydrogen, an amino or hydroxyl group, an HN-CO- $R_G^9$  radical, a branched or unbranched, optionally substituted  $C_1$ - $C_6$ -alkyl or  $C_1$ - $C_4$ -alkoxy radical, an optionally substituted aryl or arylalkyl radical or, independently of one another, in each case two  $R_G^5$  and  $R_G^6$  or  $R_G^7$  and  $R_G^8$  radicals together are an optionally substituted, fused-on, unsaturated or aromatic 3- to 6-membered carbocyclic or heterocyclic system which may contain up to three different or identical heteroatoms O, N, S, and

45

$R_G^9$  is a branched or unbranched, optionally substituted  $C_1$ - $C_6$ -alkyl or  $C_1$ - $C_4$ -alkoxy radical or an optionally substituted aryl, hetaryl, arylalkyl or hetarylalkyl radical.

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7. A drug comprising the structural element of the formula  $I_{GL}$



$I_{GL}$

10

where G and L have the following meanings:

L a structural element of the formula  $I_L$



$I_L$

15

where

T is a COOH group or a radical which can be hydrolyzed to COOH and

20

-U- is  $-(X_L)_a-(CR_L^1R_L^2)_b-$ ,  $-CR_L^1=CR_L^2-$ , ethynylene or  $=CR_L^1-$ , where

25

a is 0 or 1,

b is 0, 1 or 2

$X_L$  is  $CR_L^3R_L^4$ ,  $NR_L^5$ , oxygen or sulfur,

30

$R_L^1$ ,  $R_L^2$ ,  $R_L^3$ ,  $R_L^4$

are, independently of one another, hydrogen, -T, -OH,  $-NR_L^6R_L^7$ ,  $-CO-NH_2$ , a halogen radical, a branched or unbranched, optionally substituted  $C_1$ - $C_6$ -alkyl,  $C_2$ - $C_6$ -alkenyl,  $C_2$ - $C_6$ -alkynyl,  $C_3$ - $C_7$ -cycloalkyl,  $-CO-NH(C_1$ - $C_6$ -alkyl),  $-CO-N(C_1$ - $C_6$ -alkyl) $_2$  or  $C_1$ - $C_4$ -alkoxy radical, an optionally substituted  $C_1$ - $C_2$ -alkylene-T,  $C_2$ -alkenylene-T or  $C_2$ -alkynylene-T radical, an optionally substituted aryl or arylalkyl radical or, in each case independently of one another, two radicals  $R_L^1$  and  $R_L^2$  or  $R_L^3$  and  $R_L^4$  or, where appropriate,  $R_L^1$  and  $R_L^3$  together are an optionally substituted 3- to 7-membered saturated or unsaturated carbocyclic or heterocyclic system which may contain up to three different or identical heteroatoms O, N, S,

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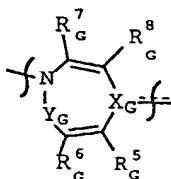
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$R_L^5, R_L^6, R_L^7$

are, independently of one another, hydrogen, a branched or unbranched, optionally substituted  $C_1-C_6$ -alkyl,  $C_3-C_7$ -cycloalkyl,  $CO-O-C_1-C_6$ -alkyl,  $SO_2-C_1-C_6$ -alkyl or  $CO-C_1-C_6$ -alkyl radical or an optionally substituted  $CO-O$ -alkylene-aryl,  $SO_2$ -aryl,  $CO$ -aryl,  $SO_2$ -alkylene-aryl or  $CO$ -alkylene-aryl radical,

G a structural element of the formula  $I_G$



$I_G$

where

the structural element G can be incorporated in both orientations, and

$X_G$  is nitrogen or  $CR_G^1$  in the case where structural element G is connected to structural element L or B via  $X_G$  by a single bond,

or

carbon in the case where structural element G is connected to structural element L via  $X_G$  by a double bond,

$Y_G$  is  $CO$ ,  $CS$ ,  $C=NR_G^2$  or  $CR_G^3R_G^4$ ,

where

$R_G^1$  is hydrogen, halogen, a hydroxyl group or a branched or unbranched, optionally substituted  $C_1-C_6$ -alkyl or  $C_1-C_4$ -alkoxy radical,

$R_G^2$  is hydrogen, a hydroxyl group, a branched or unbranched, optionally substituted  $C_1-C_6$ -alkyl,  $C_1-C_4$ -alkoxy,  $C_3-C_7$ -cycloalkyl or  $-O-C_3-C_7$ -cycloalkyl radical or an optionally substituted aryl,  $-O$ -aryl, arylalkyl or  $-O$ -alkylene-aryl radical and

$R_G^3, R_G^4$ 

are, independently of one another, hydrogen or a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkynyl or C<sub>1</sub>-C<sub>4</sub>-alkoxy radical or the two R<sub>G</sub><sup>3</sup> and R<sub>G</sub><sup>4</sup> radicals together are a cyclic acetal -O-CH<sub>2</sub>-CH<sub>2</sub>-O- or -O-CH<sub>2</sub>-O- or the two R<sub>G</sub><sup>3</sup> and R<sub>G</sub><sup>4</sup> radicals together are an optionally substituted C<sub>3</sub>-C<sub>7</sub>-cycloalkyl radical,

10  $R_G^5, R_G^6, R_G^7, R_G^8$

are, independently of one another, hydrogen, an amino or hydroxyl group, an  $\text{HN-CO-R}_G^9$  radical, a branched or unbranched, optionally substituted  $\text{C}_1\text{-C}_6\text{-alkyl}$  or  $\text{C}_1\text{-C}_4\text{-alkoxy}$  radical, an optionally substituted aryl or arylalkyl radical or, independently of one another, in each case two  $\text{R}_G^5$  and  $\text{R}_G^6$  or  $\text{R}_G^7$  and  $\text{R}_G^8$  radicals together are an optionally substituted, fused-on, unsaturated or aromatic 3- to 6-membered carbocyclic or heterocyclic system which may contain up to three different or identical heteroatoms O, N, S, and

R<sub>G</sub><sup>9</sup> is a branched or unbranched, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl or C<sub>1</sub>-C<sub>4</sub>-alkoxy radical or an optionally substituted aryl, hetaryl, arylalkyl or hetarylalkyl radical.

8. A pharmaceutical preparation for oral or parenteral use, comprising at least one compound as claimed in any of claims 1 to 5 in addition to conventional pharmaceutical excipients.
9. The use of the compounds as claimed in any of claims 1 to 5 for producing drugs for the treatment of diseases.
10. The use of the compounds as claimed in any of claims 1 to 5 as integrin receptor ligands.
11. The use as claimed in claim 10 of the compounds as claimed in any of claims 1 to 5 as ligands of the  $\alpha_v\beta_3$  integrin receptor.
12. The use as claimed in claim 9 of the compounds as claimed in any of claims 1 to 5 for producing drugs for the treatment of diseases in which the interaction between integrins and their natural ligands is excessive.



13. The use as claimed in claim 12 of the compounds as claimed in any of claims 1 to 5 for the treatment of diseases in which the interaction between  $\alpha_v\beta_3$  integrin and its natural ligands is excessive.

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14. The use as claimed in claim 13 of the compounds as claimed in any of claims 1 to 5 for the treatment of atherosclerosis, restenosis after vessel injury, angioplasty, acute kidney failure, angiogenesis-associated microangiopathies, arterial thrombosis, stroke, angiogenesis, tumor growth and metastasis, cancer, osteoporosis, high blood pressure, psoriasis or viral, parasitic or bacterial diseases, inflammations, hyperparathyroidism, Paget's disease, malignant hypercalcemia or metastatic osteolytic lesions.

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## Novel integrin receptor antagonists

## Abstract

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The invention relates to novel compounds which bind to integrin receptors, and to the preparation thereof and the use thereof as drugs.

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PA 90639 W

## DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

NOVEL ANTAGONISTS OF INTEGRIN RECEPTORS

the specification of which:

[ ] is attached hereto.

[X] was filed on Unassigned as 10/049,266

[X] was filed as PCT/EP00/07440 on August 1, 2000

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

[ ] In compliance with this duty, attached is an information disclosure statement.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, § 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed	
			Yes	No
<u>199 36 780.9</u>	<u>Germany</u>	<u>8/9/99</u>	[X]	[ ]
Number	Country	Date Filed		

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, § 1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application:



\*\*\*\*\*

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